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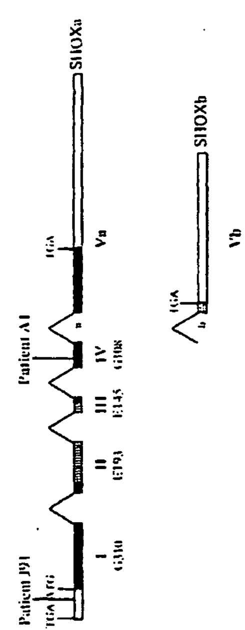
(54) Human growth gene and short stature gene region. Therapeutic uses

(57) Subject of the present invention is an isolated human nucleic acid molecule encoding polypeptides containing a homeobox domain of sixty amino acids having the amino acid sequence of SEQ ID NO: 1 and having regulating activity on human growth.

Three novel genes residing within the about 500kb short stature critical region on the X and Y chromosome were identified. At least one of these genes is responsible for the short stature phenotype. The cDNA corresponding to this gene may be used in diagnostic tools, and to further characterize the molecular basis for the short stature-phenotype. In addition, the identification of the gene product of the gene provides new means and methods for the development of superior therapies for short stature.

Fig. 1



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Description

[0001] The present invention relates to the isolation, identification and characterization of newly identified human genes responsible for disorders relating to human growth, especially for short stature or Turner syndrome, as well as the diagnosis and therapy of such disorders.

[0002] The isolated genomic DNA or fragments thereof can be used for pharmaceutical purposes or as diagnostic tools or reagents for identification or characterization of the genetic defect involved in such disorders. Subject of the present invention are further human growth proteins (transcription factors A, B and C) which are expressed after transcription of said DNA into RNA or mRNA and which can be used in the therapeutic treatment of disorders related to mutations in said genes. The invention further relates to appropriate cDNA sequences which can be used for the preparation of recombinant proteins suitable for the treatment of such disorders. Subject of the invention are further plasmid vectors for the expression of the DNA of these genes and appropriate cells containing such DNAs. It is a further subject of the present invention to provide means and methods for the genetic treatment of such disorders in the area of molecular medicine using an expression plasmid prepared by incorporating the DNA of this invention downstream from an expression promotor which effects expression in a mammalian host cell.

[0003] Growth is one of the fundamental aspects in the development of an organism, regulated by a highly organised and complex system. Height is a multifactorial trait, influenced by both environmental and genetic factors. Developmental malformations concerning body height are common phenomena among humans of all races. With an incidence of 3 in 100, growth retardation resulting in short stature account for the large majority of inborn deficiencies seen in humans.

[0004] With an incidence of 1:2500 life-born phenotypic females, Turner syndrome is a common chromosomal disorder (Rosenfeld et al., 1996). It has been estimated that 1-2% of all human conceptions are 45,X and that as many as 99 % of such fetuses do not come to term (Hall and Gilchrist, 1990; Robins, 1990). Significant clinical variability exists in the phenotype of persons with Turner syndrome (or Ullrich-Turner syndrome) (Ullrich, 1930; Turner, 1938). Short stature, however, is a consistent finding and together with gonadal dysgenesis considered as the lead symptoms of this disorder. Turner syndrome is a true multifactorial disorder. Both the embryonic lethality, the short stature, gonadal dysgenesis and the characteristic somatic features are thought to be due to monosomy of genes common to the X and Y chromosomes. The diploid dosis of those X-Y homologous genes are suggested to be requested for normal human development. Turner genes (or anti-Turner genes) are expected to be expressed in females from both the active and inactive X chromosomes or Y chromosome to ensure correct dosage of gene product. Haploinsufficiency (deficiency due to only one active copy), consequently would be the suggested genetic mechanism underlying the disease.

[0005] A variety of mechanisms underlying short stature have been elucidated so far. Growth hormone and growth hormone receptor deficiencies as well as skeletal disorders have been described as causes for the short stature phenotype (Martial et al., 1979; Phillips et al., 1981; Leung et al., 1987; Goddard et al., 1995). Recently, mutations in three human fibroblast growth factor receptor-encoding genes (FGFR 1-3) were identified as the cause of various skeletal disorders, including the most common form of dwarfism, achondroplasia (Shiang et al., 1994; Rousseau et al., 1994; Muenke and Schell, 1995). A well-known and frequent (1:2500 females) chromosomal disorder, Turner Syndrome (45,X), is also consistently associated with short stature. Taken together, however, all these different known causes account for only a small fraction of all short patients, leaving the vast majority of short stature cases unexplained to date.

[0006] The sex chromosomes X and Y are believed to harbor genes influencing height (Ogata and Matsuo, 1993). This could be deduced from genotype-phenotype correlations in patients with sex chromosome abnormalities. Cytogenetic studies have provided evidence that terminal deletions of the short arms of either the X or the Y chromosome consistently lead to short stature in the respective individuals (Zuffardi et al., 1982; Curry et al., 1984). More than 20 chromosomal rearrangements associated with terminal deletions of chromosome Xp and Yp have been reported that localize the gene(s) responsible for short stature to the pseudoautosomal region (PAR1) (Ballabio et al., 1989, Schaefer et al., 1993). This localisation has been narrowed down to the most distal 700 kb of DNA of the PAR1 region, with DXYS15 as the flanking marker (Ogata et al., 1992; 1995).

[0007] Mammalian growth regulation is organized as a complex system. It is conceivable that multiple growth promoting genes (proteins) interact with one another in a highly organized way. One of those genes controlling height has tentatively been mapped to the pseudoautosomal region PAR1 (Ballabio et al., 1989), a region known to be freely exchanged between the X and Y chromosomes (for a review see Rappold, 1993). The entire PAR1 region is approximately 2,700kb.

[0008] The critical region for short stature has been defined with deletion patients. Short stature is the consequence when an entire 700kb region is deleted or when a specific gene within this critical region is present in haploid state, is interrupted or mutated (as is the case with idiotypic short stature or Turner sydrome). The frequency of Turner's syndrome is 1 in 2500 females worldwide; the frequency of this kind of idiopathic short stature can be estimated to be 1 in 4.000 - 5.000 persons. Turner females and some short stature individuals usually receive an unspecific treatment with growth hormone (GH) for many years to over a decade although it is well known that they have normal GH levels

and GH deficiency is not the problem. The treatment of such patients is very expensive (estimated costs approximately 30.000 USD p.a.). Therefore, the problem existed to provide a method and means for distinguishing short stature patients on the one side who have a genetic defect in the respective gene and on the other side patients who do not have any genetic defect in this gene. Patients with a genetic defect in the respective gene - either a complete gene deletion (as in Turner syndrome) or a point mutation (as in idiopathic short stature) - should be susceptible for an alternative treatment without human GH, which now can be devised.

[0009] Genotype/phenotype correlations have supported the existence of a growth gene in the proximal part of Yq and in the distal part of Yp. Short stature is also consistently found in individuals with terminal deletions of Xp. Recently, an extensive search for male and female patients with partial monosomies of the pseudoautosomal region has been undertaken. On the basis of genotype-phenotype correlations, a minimal common region of deletion of 700 kb DNA adjacent to the telomere was determined (Ogata et al., 1992; Ogata et al., 1995). The region of interest was shown to lie between genetic markers DXYS20 (3cosPP) and DXYS15 (113D) and all candidate genes for growth control from within the PAR1 region (e.g., the hemopoietic growth factor receptor a; CSF2RA) (Gough et al., 1990) were excluded based on their physical location (Rappold et al., 1992). That is, the genes were within the 700 kb deletion region of the 2.700 kb PAR1 region.

[0010] Deletions of the pseudoautosomal region (PAR1) of the sex chromosomes were recently discovered in individuals with short stature and subsequently a minimal common deletion region of 700 kb within PAR1 was defined. Southern blot analysis on DNA of patients AK and SS using different pseudoautosomal markers has identified an Xp terminal deletion of about 700 kb distal to DXYS15 (113D) (Ogata et al, 1992; Ogata et al, 1995).

[0011] The gene region corresponding to short stature has been identified as a region of approximately 500 kb, preferably approximately 170 kb in the PAR1 region of the X and Y chromosomes. Three genes in this region have been identified as candidates for the short stature gene. These genes were designated SHOX (also referred to as SHOX93 or HOX93), (SHOX = short stature homeobox-containing gene), pET92 and SHOT (SHOX-like homeobox gene on chromosome three). The gene SHOX which has two separate splicing sites resulting in two variations (SHOX a and b) is of particular importance. In preliminary investigations, essential parts of the nucleotide sequence of the short stature gene could be analysed (SEQ ID No. 8). Respective exons or parts thereof could be predicted and identified (e.g. exon I [G310]; exon II [ET93]; exon IV [G108]; pET92). The obtained sequence information could then be used for designing appropriate primers or nucleotide probes which hybridize to parts of the SHOX gene or fragments thereof. By conventional methods, the SHOX gene can then be isolated. By further analysis of the DNA sequence of the genes responsible for short stature, the nucleotide sequence of exons I - V could be refined (v. fig. 1 - 3). The gene SHOX contains a homeobox sequence (SEQ ID NO: 1) of approximately 180 bp (v. fig. 2 and fig. 3), starting from the nucleotide coding for amino acid position 117 (Q) to the nucleotide coding for amino acid position 176 (E), i.e. from CAG (440) to GAG (619). The homeobox sequence is identified as the homeobox-pET93 (SHOX) sequence and two point mutations have been found in individuals with short stature in a German (A1) and a Japanese patient by screening up to date 250 individuals with idiopahtic short stature. Both point mutations were found at the identical position and leading to a protein truncation at amino acid position 195, suggesting that there may exist a hot spot of mutation. Due to the fact that both mutations found, which lead to a protein truncation, are at the identical position, it is possible that a putative hot spot of recombination exisits with exon 4 (G108). Exon specific primers can therefore be used as indicated below, e.g. GCA CAG CCA ACC ACC TAG (for) or TGG AAA GGC ATC ATC CGT AAG (rev).

[0012] The above-mentioned novel homeobox-containing gene, SHOX, which is located within the 170 kb interval, is alternatively spliced generating two proteins with diverse function. Mutation analysis and DNA sequencing were used to demonstrate that short stature can be caused by mutations in SHOX.

[0013] The identification and cloning of the short stature critical region according to the present invention was performed as follows: Extensive physical mapping studies on 15 individuals with partial monosomy in the pseudoautosomal region (PAR1) were performed. By correlating the height of those individuals with their deletion breakpoints a short stature (SS) critical region of approximately 700 kb was defined. This region was subsequently cloned as an overlapping cosmid contig using yeast artificial chromosomes (YACs) from PAR 1 (Ried et al., 1996) and by cosmid walking. To search for candidate genes for SS within this interval, a variety of techniques were applied to an approximately 600 kb region between the distal end of cosmid 56G10 and the proximal end of 51D11. Using cDNA selection, exon trapping, and CpG island cloning, the two novel genes were identified.

[0014] The position of the short stature critical interval could be refined to a smaller interval of 170 kb of DNA by characterizing three further specific individuals (GA, AT and RY), who were consistently short. To precisely localize the rearrangement breakpoints of those individuals, fluorescence *in situ* hybridization (FISH) on metaphase chromosomes was carried out using cosmids from the contig. Patient GA, with a terminal deletion and normal height, defined the distal boundary of the critical region (with the breakpoint on cosmid 110E3), and patient AT, with an X chromosome inversion and normal height, the proximal boundary (with the breakpoint on cosmid 34F5). The Y-chromosomal breakpoint of patient RY, with a terminal deletion and short stature, was also found to be contained on cosmid 34F5, suggesting that this region contains sequences predisposing to chromosome rearrangements.

[0015] The entire region, bounded by the Xp/Yp telomere, has been cloned as a set of overlapping cosmids. Fluorescence in situ hybridization (FISH) with cosmids from this region was used to study six patients with X chromosomal rearrangements, three with normal height and three with short stature. Genotype-phenotype correlations narrowed down the critical short stature interval to 270 kb of DNA or even less as 170 kb, containing the gene or genes with an important role in human growth. A minimal tiling path of six to eight cosmids bridging this interval is now available for interphase and metaphase FISH providing a valuable tool for diagnostic investigations on patients with idiopathic short stature.

Brief Description of the Drawings

[0016] Figure 1 is a gene map of the SHOX gene including five exons which are identified as follows: exon I: G310, exon II: ET93, exon III: ET45, exon IV: G108 and exons Va and Vb, whereby exons Va and Vb result from two different splicing sites of the SHOX gene. Exon II and III contain the homeobox sequence of 180 nucleotides.

[0017] Figures 2 and 3 are the nucleotide and predicted amino acid sequences of *SHOXa* and *SHOXb*:

SHOX a: The predicted start of translation begins at nucleotide 92 with the first in-frame stop codon (TGA) at nucleotides 968 - 970, yielding an open reading frame of 876 bp that encodes a predicted protein of 292 amino acids (designated as transcription factor A or SHOXa protein, respectively). An in-frame, 5'stop codon at nucleotide 4, the start codon and the predicted termination stop codon are in bold. The homeobox is boxed (starting from amino acid position 117 (Q) to 176 (E), i.e. CAG thru GAG in the nucleotide sequence). The locations of introns are indicated with arrows. Two putative polyadenylation signals in the 3'untranslated region are underlined.

SHOX b: An open reading frame of 876 bp exists from A in the first methionin at nucleotide 92 to the in-frame stop codon at nucleotide 767-769, yielding an open reading frame of 675 bp that encodes a predicted protein of 225 amino acids (transcription factor B or SHOXb protein, respectively). The locations of introns are indicated with arrows. Exons I-IV are identical with SHOXa, exon V is specific for SHOX b. A putative polyadenylation signal in the 3' untranslated region is underlined.

[0018] Figure 4 are the nucleotide and predicted amino acid sequence of SHOT. The predicted start of translation begins at nucleotide 43 with the first in-frame stop codon (TGA) at nucleotides 613 - 615, yielding an open reading frame of 573 bp that encodes a predicted protein of 190 amino acids (designated as transcription factor C or SHOT protein, respectively). The homeobox is boxed (starting from amino acid position 11 (Q) to 70 (E), i.e. CAG thru GAG in the nucleotide sequence). The locations of introns are indicated with arrows. Two putative polyadenylation signals in the 3'untranslated region are underlined

[0019] Figure5 gives the exon/intron organization of the human SHOX gene and the respective positions in the nucleotide sequence.

Brief Description of the SEQ ID:

[0020]

SEQ ID NO. 1: translated amino acid sequence of the homeobox domain (180 bp)
SEQ ID NO. 2: exon II (ET93) of the SHOX gene
SEQ ID NO. 3: exon I (G310) of the SHOX gene
SEQ ID NO. 4: exon III (ET45) of the SHOX gene
SEQ ID NO. 5: exon IV (G108) of the SHOX gene
SEQ ID NO. 6: exon Va of the SHOX gene
SEQ ID NO. 7: exon Vb of the SHOX gene
SEQ ID NO. 8: preliminary nucleotide sequence of the SHOX gene
SEQ ID NO. 9: ET92 gene
SEQ ID NO. 10: SHOXa sequence (see also fig. 2)
SEQ ID NO. 11: transcription factor A (see also fig. 2)
SEQ ID NO. 12: SHOXb sequence (see also fig. 3)
SEQ ID NO. 13: transcription factor B (see also fig 3)
SEQ ID NO. 14: SHOX gene
SEQ ID NO. 15: SHOT sequence (see also fig. 4)
SEQ ID NO. 16: transcription factor C (see also fig. 4)

[0021] Since the target gene leading to disorders in human growth (e.g. short stature region) was unknown prior to the present invention, the biological and clinical association of patients with this deletion could give insights to the function of this gene. In the present study, fluorescence in situ hybridization (FISH) was used to examine metaphase and interphase lymphocyte nuclei of six patients. The aim was to test all cosmids of the overlapping set for their utility as FISH probes and to determine the breakpoint regions in all four cases, thereby determining the minimal critical region for the short stature gene.

[0022] Duplication and deletion of genomic DNA can be technically assessed by carefully controlled quantitative PCR or dose estimation on Southern blots or by using RFLPs. However, a particularly reliable method for the accurate distinction between single and double dose of markers is FISH, the clinical application of is presently routine. Whereas in interphase FISH, the pure absence or presence of a molecular marker can be evaluated, FISH on metaphase chromosomes may provide a semi-quantitative measurement of inter-cosmid deletions. The present inventor has determined that deletions of about 10 kb (25% of signal reduction) can still be detected. This is of importance, as practically all disease genes on the human X chromosome have been associated with smaller and larger deletions in the range from a few kilobases to several megabases of DNA (Nelson et al., 1995).

[0023] Subject of the present invention are therefore DNA sequences or fragments thereof which are part of the genes responsible for human growth (or for short stature, respectively, in case of genetic defects in these genes). Three genes responsible for human growth were identified: SHOX, pET92 and SHOT. DNA sequences or fragments of these genes, as well as the respective full length DNA sequences of these genes can be transformed in an appropriate vector and transfected into cells. When such vectors are introduced into cells in an appropriate way as they are present in healthy humans, it is devisable to treat diseases involved with short stature, i.e. Turners syndrome, by modern means of gene therapy. For example, short stature can be treated by removing the respective mutated growth genes responsible for short stature. It is also possible to stimulate the respective genes which compensate the action of the genes responsible for short stature, i.e. by inserting DNA sequences before, after or within the growth/short stature genes in order to increase the expression of the healthy allels. By such modifications of the genes, the growth/short stature genes become activated or silent, respectively. This can be accomplished by inserting DNA sequences at appropriate sites within or adjacent to the gene, so that these inserted DNA sequences interfere with the growth/short stature genes and thereby activate or prevent their transcription. It is also devisable to insert a regulatory element (e.g. a promotor sequence) before said growth genes to stimulate the genes to become active. It is further devisable to stimulate the respective promotor sequence in order to overexpress - in the case of Turner syndrome - the healthy functional allele and to compensate for the missing allele. The modification of genes can be generally achieved by inserting exogenous DNA sequences into the growth gene / short stature gene via homologous recombination.

[0024] The DNA sequences according to the present invention can also be used for transformation of said sequences into animals, such as mammals, via an appropriate vector system. These transgenic animals can then be used for *in vivo* investigations for screening or identifying pharamceutical agents which are useful in the treatment of diseases involved with short stature. If the animals positively respond to the administration of a candidate compound or agent, such agent or compound or derivatives thereof would be devisable as pharmaceutical agents. By appropriate means, the DNA sequences of the present invention can also be used in genetic experiments aiming at finding methods in order to compensate for the loss of genes responsible for short stature (knock-out animals).

[0025] In a further object of this invention, the DNA sequences can also be used to be transformed into cells. These cells can be used for identifying pharmaceutical agents useful for the treatment of diseases involved with short stature, or for screening of such compounds or library of compounds. In an appropriate test system, variations in the phenotype or in the expression pattern of these cells can be determined, thereby allowing the identification of interesting candidate agents in the development of pharmaceutical drugs.

[0026] The DNA sequences of the present invention can also be used for the design of appropriate primers which hybridize with segments of the short stature genes or fragments thereof under stringent conditions. Appropriate primer sequences can be constructed which are useful in the diagnosis of people who have a genetic defect causing short stature. In this respect it is noteworthy that the two mutations found occur at the identical position, suggesting that a mutational hot spot exists.

[0027] In general, DNA sequences according to the present invention are understood to embrace also such DNA sequences which are degenerate to the specific sequences shown, based on the degeneracy of the genetic code, or which hybridize under stringent conditions with the specifically shown DNA sequences.

[0028] The present invention encompasses especially the following aspects:

a) An isolated human nucleic acid molecule encoding polypeptides containing a homeobox domain of sixty amino acids having the amino acid sequence of SEQ ID NO: 1 and having regulating activity on human growth.
b) An isolated DNA molecule comprising the nucleotide sequence essentially as indicated in fig. 2, fig. 3 or fig. 4, and especially as shown in SEQ ID NO: 10, SEQ ID NO: 12 or SEQ ID NO: 15.
c) DNA molecules capable of hybridizing to the DNA molecules of item b).

d) DNA molecules of item c) above which are capable of hybridization with the DNA molecules of item 2. under a temperature of 60 - 70 °C and in the presence of a standard buffer solution.

e) DNA molecules comprising a nucleotide sequence having a homology of seventy percent or higher with the nucleotide sequence of SEQ ID NO: 10, SEQ ID NO: 12 or SEQ ID NO: 15and encoding a polypeptide having regulating activity on human growth.

f) Human growth proteins having the amino acid sequence of SEQ ID NO: 11, 13 or 16 or a functional fragment thereof.

g) Antibodies obtained from immunization of animals with human growth proteins of item f) or antigenic variants thereof.

h) Pharmaceutical compositions comprising human growth proteins or functional fragments thereof for treating disorders caused by genetic mutations of the human growth gene.

i) A method of screening for a substance effective for the treatment of disorders mentioned above under item h) comprising detecting messenger RNA hybridizing to any of the DNA molecules decribed in a) - e) so as to measure any enhancement in the expression levels of the DNA molecule in response to treatment of the host cell with that substance.

j) An expression vector or plasmid containing any of the nucleic acid molecules described in a) - e) above which enables the DNA molecules to be expressed in mammalian cells.

k) A method for the determination of the gene or genes responsible for short stature in a biological sample of body tissues or body fluids.

[0029] In the method k) above, preferably nucleotide amplification techniques, e.g. PCR, are used for detecting specific nucleotide sequences known to persons skilled in the art, and described, for example, by Mullis et al. 1986, Cold Spring Harbor Symposium Quant. Biol. 51, 263-273, and Saiki et al., 1988, Science 239, 487-491, which are incorporated herein by reference. The short stature nucleotide sequences to be determined are mainly those represented by sequences SEQ ID No. 2 to SEQ ID No. 7.

[0030] In principle, all oligonucleotide primers and probes for amplifying and detecting a genetic defect responsible for deminished human growth in a biological sample are suitable for amplifying a target short stature associated sequence. Especially, suitable exon specific primer pairs according to the invention are provided by table 1. Subsequently, a suitable detection, e.g. a radioactive or non-radioactive label is carried out.

Table 1:

Exon	Sense primer	Antisense primer	Product (bp)	Ta (°C)
5'-I (G310)	SP 1	ASP 1	194	58
3'-I (G310)	SP 2	ASP 2	295	58
II (ET93)	SP 3	ASP 3	262	76/72/68
III (ET45)	SP 4	ASP 4	120	65
IV (G108)	SP 5	ASP 5	154	62
Va (SHOXa)	SP 6	ASP 6	265	61

explanation of the abbreviations for the primers:

SP 1 : ATTTCCAATGGAAAGGCGTAAATAAC
SP2 : ACGGCTTTTGTATCCAAGTCTTTTG
SP3 : GCCCTGTGCCCTCCGCTCCC
SP4 : GGCTCTTCACATCTCTCTCTGCTTC
SP5 : CCACACTGACACCTGCTCCCTTTG
SP6 : CCCGCAGGTCCAGGCTCAGCTG
ASP1 : CGCCTCCGCCGTTACCGTCCTTG
ASP 2 : CCCTGGAGCCGGCGCGCAAAG
ASP 3 : CCCCGCCCCCGCCCCCGG
ASP 4 : CTTCAGGTCCCCCCAGTCCCG
ASP 5 : CTAGGGATCTTCAGAGGAAGAAAAAG
ASP 6 : GCTGCGCGGCGGGTCAGAGCCCCAG

[0031] Also, a single stranded RNA can be used as target. Methods for reversed transcribing RNA into cDNA are also well known and described in Sambrook et al., Molecular Cloning: A Laboratory Manual, New York, Cold Spring Harbor Laboratory 1989. Alternatively, preferred methods for reversed transcription utilize thermostable DNA polymerases having RT activity.

[0032] Further, the technique described before can be used for selecting those person from a group of persons being of short stature characterized by a genetic defect and which allows as a consequence a more specific medical treatment.

[0033] In another subject of the present invention, the transcription factors A, B and C can be used as pharmaceutical agents. These transcription factors initiate a still unknown cascade of biological effects on a molecular level involved with human growth. These proteins or functional fragments thereof have a mitogenic effect on various cells. Especially, they have an osteogenic effect. They can be used in the treatment of bone diseases, such as e.g. osteoporosis, and especially all those diseases involved with disturbance in the bone calcium regulation.

[0034] As used herein, the term "isolated" refers to the original derivation of the DNA molecule by cloning. It is to be understood however, that this term is not intended to be so limiting and, in fact, the present invention relates to both naturally occurring and synthetically prepared seqences, as will be understood by the skilled person in the art.

[0035] The DNA molecules of this invention may be used in forms of gene therapy involving the use of an expression

plasmid prepared by incorporating an appropriate DNA sequence of this invention downstream from an expression promotor that effects expression in a mammalian host cell. Suitable host cells are procaryotic or eucaryotic cells. Procaryotic host cells are, for example, E. coli, Bacillus subtilis, and the like. By transfecting host cells with replicons originating from species adaptable to the host, that is, plasmid vectors containing replication starting point and regulator sequences, these host cells can be transfected with the desired gene or cDNA. Such vectors are preferably those having a sequence that provides the transfected cells with a property (phenotype) by which they can be selected. For example, for E. coli hosts the strain E. coli K12 is typically used, and for the vector either pBR322 or pUC plasmids can be generally employed. Examples for suitable promotors for E. coli hosts are trp promotor, lac promotor or lpp promotor. If desired, secretion of the expression product through the cell membrane can be effected by connecting a DNA sequence coding for a signal peptide sequence at the 5' upstream side of the gene. Eucaryotic host cells include cells derived from vertebrates or yeast etc.. As a vertebrate host cell, COS cells can be used (Cell, 1981, 23: 175 - 182), or CHO cells. Preferably, promotors can be used which are positioned 5' upstream of the gene to be expressed and having RNA splicing positions, polyadenylation and transcription termination seqences.

[0036] The transcription factors A, B and C of the present invention can be used to treat disorders caused by mutations in the human growth genes and can be used as growth promoting agents. Due to the polymorphism known in the case of eukaryotic genes, one or more amino acids may be substituted. Also, one or more amino acids in the polypeptides can be deleted or inserted at one or more sites in the amino acid sequence of the polypeptides of SEQ ID NO: 11, 13 or 16. Such polypeptides are generally referred to equivalent polypeptides as long as the underlying biological acitivity of the unmodified polypeptide remains essentially unchanged.

[0037] The present invention is illustrated by the following examples.

Example 1

Patients

[0038] All six patients studied had de novo sex chromosome aberrations.

[0039] CC is a girl with a karyotype 45,X/46,X psu dic (X) (Xqter → Xp22.3::Xp22.3 → Xqter). At the last examination at 6 1/2 years of age, her height was 114 cm (25 - 50 the % percentile). Her mother's height was 155 cm, the father was not available for analysis. For details, see Henke et al., 1991.

[0040] GA is a girl with a karyotype 46,X der X (3pter → 3p23::Xp22.3 → Xqter). At the last examination at 17 years, normal stature (159 cm) was observed. Her mother's height is 160 cm and her father's height 182 cm. For details, see Kulharya et al, 1995.

[0041] SS is a girl with a karyotype 46,X rea (X) (Xqter → Xq26 :: Xp22.3 → Xq26:). At 11 years her height remained below the 3rd percentile growth curve for Japanese girls; her predicted adult height (148.5 cm) was below her target height (163 cm) and target range (155 to 191 em). For details, see Ogata et alt, 1992.

[0042] AK is a girl with a karyotype 46,X rea (X) (Xqter → Xp22.3::Xp22.3 → Xp21.3:). At 13 years her height remained below the 2nd percentile growth curve for Japanese girls; her predicted adult height (142.8 cm) was below her target height (155.5 cm) and target range (147.5 - 163.5 em). For details, see Ogata et alt, 1995.

[0043] RY: the karyotype of the ring Y patient is 46,X,r(Y)/46,Xdic r(Y)/45,X[95:3:2], as examined on 100 lymphocytes; at 16 years of age his final height was 148; the heights of his three brothers are all in the normal range with 170 cm (16 years, brother 1), 164 cm (14 years, brother 2) and 128 cm (9 years, brother 3), respectively. Growth retardation of this patient is so severe that it would also be compatible with an additional deletion of the GCY locus on Yq.

[0044] AT: boy with ataxia and inv(X); normal height of 116 cm at age 7, parents' heights are 156 cm and 190 cm, respectively.

Patients for mutation analysis:

[0045] 250 individuals with idiopathic short stature were tested for mutations in SHOXa. The patients were selected on the following criteria: height for chronological age was below the 3rd centile of national height standards, minus 2 standard deviations (SDS); no causative disease was known, in particular: normal weight (length) for gestational age, normal body proportions, no chronic organic disorder, normal food intake, no psychiatric disorder, no skeletal dysplasia disorder, no thyroid or growth hormone deficiency.

Family A:

[0046] Cases 1 and 2 are short statured children of a German non-consanguineous family. The boy (case 1) was born at the 38th week of gestation by cesarian section. Birth weight was 2660 g, birth length 47 cm. He developed normally except for subnormal growth. On examination at the age of 6.4 years, he was proportionate small (106.8 cm,

-2.6 SDS) and obese (22.7 kg), but otherwise normal. His bone age was not retarded (6 yrs) and bone dysplasia was excluded by X-ray analysis. IGF-I and IGFBP-3 levels as well as thyroid parameters in serum rendered GH or thyroid hormone deficiency unlikely. The girl (case 2) was born at term by cesarian section. Birth weight was 2920 g, birth length 47 cm. Her developmental milestones were normal, but by the age of 12 months poor growth was apparent (length: 67 cm, -3.0 SDS). At 4 years she was 89.6 cm of height (-3.6 SDS). No dysmorphic features or dysproportions were apparent. She was not obese (13 kg). Her bone age was 3.5 years and bone dysplasia was excluded. Hormone parameters were normal. It is interesting to note that both the girl and the boy grow on the 50 percentile growth curve for females with Turner syndrome. The mother is the smallest of the family and has a mild rhizomelic dysproportion (142.3 cm, -3.8 SDS). One of her two sisters (150 cm, -2.5 SDS) and the maternal grandmother (153 cm, -2.0 SDS) are all short without any dysproportion. One sister has normal stature (167 cm, +0.4 SDS). The father's height is 166 cm (-1.8 SDS) and the maternal grandfather' height is 165 cm (-1.9 SDS). The other patient was of Japanese origin and showed the identical mutation.

Example 2

Identification of the short stature gene

A. In situ hybridization

a) Florescence in situ hybridization (FISH)

[0047] Florescence in situ hybridization (FISH) using cosmids residing in the Xp/Yp pseudoautosomal region (PAR1) was carried out. FISH studies using cosmids 64/75cos (LLNLc110H032), E22cos (2e2), F1/14cos (110A7), M1/70cos (110E3), P99F2cos (43C11), P99cos (LLNLc110P2410), B6cosb (1CRFc104H0425), F20cos (34F5), F21cos (ICRFc104G0411), F3cos2 (9E3), F3cosl (11E6), P117cos (29B11), P6cosl (ICRFc104P0117), P6cos2 (LLNLc110E0625) and E4cos (15G7) was carried out according to published methods (Lichter and Cremer, 1992). In short, one microgram of the respective cosmid clone was labeled with biotin and hybridized to human metaphase chromosomes under conditions that suppress signals from repetitive DNA sequences. Detection of the hybridization signal was via FITC-conjugated avidin. Images of FITC were taken by using a cooled charge coupled device camera system (Photometrics, Tucson, AZ).

b) Physical mapping

[0048] Cosmids were derived from Lawrence Livermore National Laboratory X- and Y-chromosome libraries and the Imperial Cancer Research Fund London (now Max Planck Institute for Molecular Genetics Berlin) X chromosome library. Using cosmids distal to DXYS15, namely E4cos, P6cos2, P6cosl, P117cos and F3cosl one can determine that two copies are still present of E4cos, P6cos2, P6cos1 and one copy of P117cos and F3cos1. Breakpoints of both patients AK and SS map on cosmid P6cos1, with a maximum physical distance of 10 kb from each other. It was concluded that the abnormal X chromosomes of AK and SS have deleted about 630 kb of DNA.

[0049] Further cosmids were derived from the ICRF X chromosome specific cosmid library (ICRFc104), the Lawrence Livermore X chromosome specific cosmid library (LLNLc110) and the Y chromosome specific library (LLCO3'M'), as well as from a self-made cosmid library covering the entire genome. Cosmids were identified by hybridisation with all known probes mapping to this region and by using entire YACs as probes. To verify overlaps, end probes from several cosmids were used in cases in which overlaps could not be proven using known probes.

c) Southern Blot Hybridisation

[0050] Southern blot analysis using different pseudoautosomal markers has provided evidence that the breakpoint on the X chromosome of patient CC resides between DXYS20 (3cosPP) and DXYS60 (U7A) (Henke et al, 1991). In order to confirm this finding and to refine the breakpoint location, cosmids 64/75cos, E22cos, F1/14cos, M1/70cos, F2cos, P99F2cos and P99cos were used as FISH probes. The breakpoint location on the abnormal X of patient CC between cosmids 64/75cos (one copy) and F1/14cos (two copies) on the E22PAC could be determined. Patient CC with normal stature consequently has lost approximately 260-290 kb of DNA.

[0051] Southern blot hybridisations were carried out at high stringency conditions in Church buffer (0.5 M NaPi pH 7.2, 7% SDS, 1mM EDTA) at 65°C and washed in 40 mM NaPi, 1% SDS at 65°C.

d) FISH Analysis

[0052] Biotinylated cosmid DNA (insert size 32 - 45 kb) or cosmid fragments (10 - 16 kb) were hybridised to metaphase chromosomes from stimulated lymphocytes of patients under conditions as described previously (Lichter and Cremer, 1992). The hybridised probe was detected via avidin-conjugated FITC.

e) PCR Amplification

[0053] All PCRs were performed in 50 μl volumes containing 100 pg-200 ng template, 20 pmol of each primer, 200 μM dNTP's (Pharmacia), 1.5 mM $MgCl_2$, 75 mMTris/HCl pH9, 20mM $(NH_4)_2SO_4$ 0.01% (w/v) Tween20 and 2 U of Goldstar DNA Polymerase (Eurogentec). Thermal cycling was carried out in a Thermocycler GeneE (Techne).

f) Exon Amplification

[0054] Four cosmid pools consisting of each four to five clones from the cosmid contigs were used for exon amplification experiments. The cosmids in each cosmid pool were partially digested with Sau3A. Gel purified fractions in the size range of 4-10 kb were cloned in the BamHI digested pSPL3B vector (Burn et al, 1995) and used for the exon amplification experiments as previously described (Church et al., 1994).

g) Genomic Sequencing

[0055] Sonificated fragments of the two cosmids LLOYNCO3'M' 15D10 and LLOYNCO3'M'34F5 were subcloned separately into M13mp18 vectors. From each cosmid library at least 1000 plaques were picked, M13 DNA prepared and sequenced using dye-terminators, ThermoSequenase (Amersham) and universal M13-primer (MWG-BioTech). The gels were run on ABI-377 sequencers and data were assembled and edited with the GAP4 program (Staden).

[0056] Of all six patients, GA had the least well characterized chromosomal breakpoint. The most distal markers previously tested for their presence or absence on the X were DXS1060 and DXS996, which map approximately 6 Mb from the telomere (Nelson et al., 1995). Several cosmids containing different gene sequences from within PAR1 (MIC2, ANT3, CSF2RA, and XE7) were tested and all were present on the translocation chromosome. Cosmids from within the short stature critical region e.g., chromosome, thereby placing the translocation breakpoint on cosmid M1/70cos. A quantitative comparison of the signal intensities of M1/70cos between the normal and the rearranged X indicates that approximately 70% of this cosmid is deleted.

TABLE 2

	CC	GA	AK	SS
64/75cos	-	-		
E22cos	-	-		
F1/14cos	+	-		
M1/70cos	+	(+)		
F2cos	+	+		
P99F2cos	+	+		
P99cos	+	+		
B6cos		+		
F20cos				
F21cos				
F3cos2				
F3cosl			-	-
P117cos			-	-
P6cosl			+	+
P6cos2			+	+

TABLE 2 (continued)

	CC	GA	AK	SS
E4cos			+	+

Table 2: This table summarizes the FISH data for the 16 cosmids tested on four patients.

[-] one copy; indicates that the respective cosmid was deleted on the rearranged X, but present on the normal X chromosome

[+] two copies; indicates that the respective cosmid is present on the rearranged and on the normal X chromosome

[(+)] breakpoint region; indicates that the breakpoint occurs within the cosmid as shown by FISH

[0057] In summary, the molecular analysis on six patients with X chromosomal rearrangements using florescence-labeled cosmid probes and in situ hybridization indicates that the short stature critical region can be narrowed down to a 270 kb interval, bounded by the breakpoint of patient GA from its centromere distal side and by patients AK and SS on its centromere proximal side.

[0058] Genotype-phenotype correlations may be informative and have been chosen to delineate the short stature critical interval on the human X and Y chromosome. In the present study FISH analysis was used to study metaphase spreads and interphase nuclei of lymphocytes from patients carrying deletions and translocations on the X chromosome and breakpoints within Xp22.3. These breakpoints appear to be clustered in two of the four patients (AK and SS) presumably due to the presence of sequences predisposing to chromosome rearrangements. One additional patient Ring Y has been found with an interruption in the 270 kb critical region, thereby reducing the critical interval to a 170 kb region.

[0059] By correlating the height of all six individuals with their deletion breakpoint, an interval of 170 kb was mapped to within the pseudoautosomal region, presence or absence of which has a significant effect on stature. This interval is bounded by the X chromosomal breakpoint of patient GA at 340 kb from the telomere (Xptel) distally and by the breakpoints of patients AT and RY at 510/520 kb Xptel proximally. This assignment constitutes a considerable reduction of the critical interval to almost one fourth of its previous size (Ogata et al., 1992; Ogata et al., 1995). A small set of six to eight cosmids are now available for FISH experiments to test for the prevalence and significance of this genomic locus on a large series of patients with idiopathic short stature.

B. Identification of the Candidate Short Stature Gene

[0060] To search for transcription units within the smallest 170 kb critical region, exon trapping and cDNA selection on six cosmids (110E3, F2cos, 43C11, P2410, 15D10, 34F5) was carried out. Three different positive clones (ET93, ET45 and G108) were isolated by exon trapping, all of which mapped back to cosmid 34F5. Previous studies using cDNA selection protocols and an excess of 25 different cDNA libraries had proven unsuccessful, suggesting that genes in this interval are expressed at very low abundancy.

[0061] To find out whether any gene in this interval was missed, the nucleotide sequence of about 140 kb from this region of the PAR1 was determined, using the random M13 method and dye terminator chemistry. The cosmids for sequence analysis were chosen to minimally overlap with each other and to collectively span the critical interval. DNA sequence analysis and subsequent protein prediction by the "X Grail" program, version 1.3c as well as by the exon-trapping program FEXHB were carried out and confirmed all 3 previously cloned exons. No protein-coding genes other than the previously isolated one could be detected.

C. Isolation of the Short Stature Candidate Gene SHOX

[0062] Assuming that all three exon clones ET93, ET45 and G108 are part of the same gene, they were used collectively as probes to screen 14 different cDNA libraries from 12 different fetal (lung, liver, brain 1 and 2) and adult tissues (ovary, placenta 1 and 2, fibroblast, skeletal muscle, bone marrow, brain, brain stem, hypothalamus, pituitary). Not a single clone among approximately 14 million plated clones was detected. To isolate the full-length transcript, 3' and 5'RACE were carried out. For 3'RACE, primers from exon G108 were used on RNA from placenta, skeletal muscle and bone marrow fibroblasts, tissues where G108 was shown to be expressed in. Two different 3'RACE clones of 1173 and 652 bp were derived from all three tissues, suggesting that two different 3'exons a and b exist. The two different forms were termed SHOXa and SHOXb.

[0063] To increase chances to isolate the complete 5'portion of a gene known to be expressed at low abundancy, a Hela cell line was treated with retinoic acid and phorbol ester PMA. RNA from such an induced cell line and RNA from

placenta and skeletal muscle were used for the construction of a 'Marathon cDNA library'. Identical 5'RACE cDNA clones were isolated from all three tissues.

Experimental procedure:

RT-PCR and cDNA Library Construction

[0064] Human polyA+RNA of heart, pancreas, placenta, skeletal muscle, fetal kidney and liver was purchased from Clontech. Total RNA was isolated from a bone marrow fibroblast cell line with TRIZOL reagent (Gibco-BRL) as described by the manufacturer. First strand cDNA synthesis was performed with the Superscript first strand cDNA synthesis kit (Gibco-BRL) starting with 100 ng polyA+RNA or 10µg total RNA using oligo(dt)-adapter primer (GGCCACGCGTC-GACTAGTAC[dT]$_{20}$N. After first strand cDNA synthesis the reaction mix was diluted 1/10. For further PCR experiments 5µl of this dilutions were used.

[0065] A 'Marathon cDNA library' was constructed from skeletal muscle and placenta polyA+RNA with the marathon cDNA amplification kit (Clontech) as described by the manufacturer.

[0066] Fetal brain (catalog # HL5015b), fetal lung (HL3022a), ovary (HL1098a), pituitary gland (HL1097v) and hypothalamus (HL1172b) cDNA libraries were purchased from Clontech. Brain, kidney, liver and lung cDNA libraries were part of the quick screen human cDNA library panel (Clontech). Fetal muscle cDNA library was obtained from the UK Human Genome Mapping Project Resource Center.

D. Sequence Analysis and Structure of SHOX Gene

[0067] A consensus sequence of SHOXa and SHOXb (1349 and 1870 bp) was assembled by analysis of sequences from the 5' and 3'RACE derived clones. A single open reading frame of 1870 bp (SHOXa) and 1349 bp (SHOXb) was identified, resulting in two proteins of 292 (SHOXa) and 225 amino acids (SHOXb). Both transcripts a and b share a common 5'end, but have a different last 3'exon, a finding suggestive of the use of alternative splicing signals. A complete alignment between the two cDNAs and the sequenced genomic DNA from cosmids LL0YNCO3"M"15D10 and LL0YNC3"M"34F5 was achieved, allowing establishment of the exon-intron structure (Fig.4). The gene is composed of 6 exons ranging in size from 58 bp (exon III) to 1146 bp (exon Va). Exon I contains a CpG-island, the start codon and the 5' region. A stop codon as well as the 3'-noncoding region is located in each of the alternatively spliced exons Va and Vb.

Example 3

[0068] Two cDNAs have been identified which map to the 160 kb region identified as critical for short stature. These cDNAs correspond to the genes SHOX and pET92. The cDNAs were identified by the hybridization of subclones of the cosmids to cDNA libraries.

[0069] Employing the set of cosmid clones with complete coverage of the critical region has now provided the genetic material to identify the causative gene. Positional cloning projects aimed at the isolation of the genes from this region are done by exon trapping and cDNA selection techniques. By virtue of their location within the pseudoautosomal region, these genes can be assumed to escape X-inactivation and to exert a dosage effect.

[0070] The cloning of the gene leading to short stature when absent (haploid) or deficient, represents a further step forward in diagnostic accuracy, providing the basis for mutational analysis within the gene by e.g. single strand conformation polymorphism (SSCP). In addition, cloning of this gene and its subsequent biochemical characterization has opened the way to a deeper understanding of biological processes involved in growth control.

[0071] The DNA sequences of the present invention provide a first molecular test to identify individuals with a specific genetic disorder within the complex heterogeneous group of patients with idiopathic short stature.

Example 4

Expression Pattern of SHOXa and SHOXb

[0072] Northern blot analysis using single exons as hybridisation probes reveiled a different expression profile for every exon, strongly suggesting that the bands of different size and intensities represent cross-hybridisation products to other G,C rich gene sequences. To achieve a more realistic expression profile of both genes SHOXa and b, RT-PCR experiments on RNA from different tissues were carried out. Whereas expression of SHOXa was observed in skeletal muscle, placenta, pancreas, heart and bone marrow fibroblasts, expression of SHOXb was restricted to fetal kidney, skeletal muscle and bone marrow fibroblasts, with the far highest expression in bone marrow fibroblasts.

[0073] The expression of SHOXa in several cDNA libraries made of fetal brain, lung and muscle, of adult brain, lung and pituitary and of SHOXb in none of the tested libraries gives additional evidence that one spliced form (SHOXa) is more broadly expressed and the other (SHOXb) expressed in a predominantly tissue-specific manner.

[0074] To assess the transcriptional activity of SHOXa and SHOXb on the X and Y chromosome we used RT-PCR of RNA extracted from various cell lines containing the active X, the inactive X or the Y chromosome as the only human chromosomes. All cell lines revealed an amplification product of the expected length of 119 bp (SHOXa) and 541 bp (SHÒXb), providing clear evidence that both SHOXa and b escape X-inactivation.

[0075] SHOXa and SHOXb encode novel homeodomain proteins. SHOX is highly conserved across species from mammalian to fish and flies. The very 5' end and the very 3' end - besides the homeodomain- are likely conserved regions between man and mouse, indicating a functional significance. Differences in those amino acid regions have not been allowed to accumulate during evolution between man and mouse.

Experimental procedures:

a) 5' and 3'RACE

[0076] To clone the 5' end of the SHOXa and b transcripts, 5'RACE was performed using the constructed 'Marathon cDNA libraries'. The following oligonucleotide primers were used: SHOX B rev, GAAAGGCATCCGTAAGGCTCCC (position 697-718, reverse strand [r]) and the adaptor primer AP1. PCR was carried out using touchdown parameters: 94°C for 2 min, 94°C for 30 sec, 70°C for 30 sec, 72°C for 2 min for 5 cycles. 94°C for 30 sec, 66°C for 30 sec, 72°C for 2 min for 5 cycles. 94°C for 30 sec, 62°C for 30 sec, 72°C for 2 min for 25 cycles. A second round of amplification was performed using 1/100 of the PCR product and the following nested oligonucleotide primers: SHOX A rev, GACGCCTTTATGCATCTGATTCTC (position 617-640 r) and the adaptor primer AP2. PCR was carried out for 35 cycles with an annealing temperature of 60°C.

[0077] To clone the 3' end of the SHOXa and b transcripts, 3'RACE was performed as previously described (Frohman et al., 1988) using oligo(dT)adaptor primed first strand cDNA. The following oligonucleotide primers were used: SHOX A for, GAATCAGATGCATAAAGGCGTC (position 619-640) and the oligo(dT)adaptor. PCR was carried out using following parameters: 94°C for 2 min, 94°C for 30 sec, 62°C for 30 sec, 72°C for 2 min for 35 cycles. A second round of amplification was performed using 1/100 of the PCR product and the following nested oligonucleotide primers: SHOX B for, GGGAGCCTTACGGATGCCTTTC (position 697-718) and the oligo(dT)adaptor. PCR was carried out for 35 cycles with annealing temperature of 62°C.

[0078] To validate the sequences of SHOXa and SHOXb transcripts, PCR was performed with a 5' oligonucleotide primer and a 3' oligonucleotide primer. For SHOXa the following primers were used: G310 for, AGCCCCGGCTGCTCGCCAGC (position 59-78) and SHOX D rev, CTGCGCGGCGGGTCAGAGCCCCAG (position 959-982 r). For SHOXb the following primers were used: G310 for, AGCCCCGGCTGCTCGCCAGC and SHOX2A rev, GCCTCAGCAGCAAAGCAAGATCCC (position 1215-1238 r). Both PCRs were carried out using touchdown parameters: 94°C for 2 min, 94°C for 30 sec, 70°C for 30 sec, 72°C for 2 min for 5 cycles. 94°C for 30 sec, 68°C for 30 sec, 72°C for 2 min for 5 cycles. 94°C for 30 sec, 65°C for 30 sec, 72°C for 2 min for 35 cycles. Products were gel-purified and cloned for sequencing analysis.

b) SSCP Analysis

[0079] SSCP analysis was performed on genomic amplified DNA from patients according to a previously described method (Orita et al., 1989). One to five µl of the PCR products were mixed with 5 µl of denaturation solution containing 95% Formamid and 10mM EDTA pH8 and denaturated at 95°C for 10 min. Samples were immediately chilled on ice and loaded on a 10% Polyacryamidgel (Acrylamide:Bisacryamide = 37.5:1 and 29:1; Multislotgel, TGGE base, Qiagen) containing 2% glycerol and 1xTBE. Gels were run at 15°C with 500V for 3 to 5 hours and silver stained as described in TGGE handbook (Qiagen, 1993).

c) Cloning and Sequencing of PCR Products

[0080] PCR products were cloned into pMOS*Blue* using the pMOS*Blue*T- Vector Kit from Amersham. Overnight cultures of single colonies were lysed in 100 µl H_2O by boiling for 10 min. The lysates were used as templates for PCRs with specific primers for the cloned PCR product. SSCP of PCR products allowed the identification of clones containing different alleles. The clones were sequenced with CY5 labelled vector primers Uni and T7 by the cycle sequencing method described by the manufacturer (ThermoSequenase Kit (Amersham)) on an ALF express automated sequencer (Pharmacia).

d) PCR Screening of cDNA Libraries

[0081] To detect expression of SHOXa and b, a PCR screening of several cDNA libraries and first strand cDNAs was carried out with SHOXa and b specific primers. For the cDNA libraries a DNA equivalent of $5x10^8$ pfu was used. For SHOXa, primers SHOX E rev, GCTGAGCCTGGACCTGTTGGAAAGG (position 713-737 r) and SHOX a for were used. For SHOXb, the following primers were used: SHOX B for and SHOX2A rev. Both PCRs were carried out using touchdown parameters: 94°C for 2 min; 94°C for 30 sec, 68°C for 30 sec, 72°C for 40 sec for 5 cycles. 94°C for 30 sec, 65°C for 30 sec, 72°C for 40 sec for 5 cycles. 94°C for 30 sec, 62°C for 30 sec, 72°C for 40 sec for 35 cycles.

e) PCR Screening of cDNA Libraries

[0082] To detect expression of SHOXa and b, a PCR screening of several cDNA libraries and first strand cDNAs was carried out with SHOXa and b specific primers. For the cDNA libraries a DNA equivalent of $5x10^8$ pfu was used. For SHOXa, primers SHOX E rev, GCTGAGCCTGGACCTGTTGGAAAGG (position 713-737 r) and SHOX a for were used. For SHOXb, the following primers were used: SHOX B for and SHOX2A rev. Both PCRs were carried out using touchdown parameters: 94°C for 2 min; 94°C for 30 sec, 68°C for 30 sec, 72°C for 40 sec for 5 cycles. 94°C for 30 sec, 65°C for 30 sec, 72°C for 40 sec for 5 cycles. 94°C for 30 sec, 62°C for 30 sec, 72°C for 40 sec for 35 cycles.

Example 5

Expression pattern of OG12, the putative mouse homolog of both SHOX and SHOT

[0083] In situ hybridisation on mouse embryos ranging from day 5 p.c. and day 18,5 p.c., as well as on fetal and newborn animals was carried out to establish the expression pattern. Expression was seen in the developing limb buds, in the mesoderm of nasal processes which contribute to the formation of the nose and palate, in the eyelid, in the aorta, in the developing female gonads, in the developing spinal cord (restricted to differentiating motor neurons) and brain. Based on this expression pattern and on the mapping position of its human homolog SHOT, SHOT represents a likely candidate for the Cornelia de Lange syndrome which includes short stature.

Example 6

[0084] Isolation of a novel SHOX-like homeobox gene on chromosome three, SHOT, being related to human growth / short stature

[0085] A new gene called SHOT (for SHOX-homolog on chromosome three) was isolated in human, sharing the most homology with the murine OG12 gene and the human SHOX gene. The human SHOT gene and the murine OG12 genes are highly homologous, with 99 % identity at the protein level. Although not yet proven, due to the striking homology between SHOT and SHOX (identity within the homeodomain only), it is likely that SHOT is also a gene likely involved in short stature or human growth.

[0086] SHOT was isolated using primers from two new human ESTs (HS 1224703 and HS 126759) from the EMBL database, to amplify a reverse-transcribed RNA from a bone marrow fibroblast line (Rao et al, 1997). The 5' and 3' ends of SHOT were generated by RACE-PCR from a bone marrow fibroblast library that was constructed according to Rao et al., 1997. SHOT was mapped by FISH analysis to chromosome 3q25/q26 and the murine homolog to the syntenic region on mouse chromosome 3. Based on the expression pattern of OG12, its mouse homolog, SHOT represents a candidate for the Cornelia Lange syndrome (which shows short stature and other features, including craniofacial abnormalities) mapped to this chromosomal interval on 3q25/26.

Example 7

Searching for Mutations in Patients with Idiopathic Short Stature

[0087] The DNA sequences of the present invention are used in PCR, LCR, and other known technologies to determine if such individuals with short stature have small deletions or point mutations in the short stature gene.

[0088] A total of initially 91 (in total 250 individuals) unrelated male and female patients with idiopathic short stature (idiopathic short stature has an estimated incidence of 2 - 2,5 % in the general population) were tested for small rearrangements or point mutations in the SHOXa gene. Six sets of PCR primers were designed not only to amplify single exons but also sequences flanking the exon and a small part of the 5'UTR. For the largest exon, exon one, two additional internal-exon primers were generated. Primers used for PCR are shown in table 2.

[0089] Single strand conformation polymorphism (SSCP) of all amplified exons ranging from 120 to 295 bp in size

was carried out. Band mobility shifts were identified in only 2 individuals with short stature (Y91 and A1). Fragments that gave altered SSCP patterns (unique SSCP conformers) were cloned and sequenced. To avoid PCR and sequencing artifacts, sequencing was performed on two strands using two independent PCR reactions. The mutation in patient Y91 resides 28bp 5'of the start codon in the 5'UTR and involves a cytidine-to-guanine substitution. To find out if this mutation represents a rare polymorphism or is responsible for the phenotype by regulating gene expression e.g. though a weaker binding of translation initiation factors, his parents and a sister were tested. As both the sister and father with normal height also show the same SSCP variant (data not shown), this base substitution represents a rare polymorphism unrelated to the phenotype.

[0090] Cloning and sequencing of a unique SSCP conformer for patient AI revealed a cytidine-to-thymidine base transition (nucleotide 674) which introduces a termination codon at amino-acid position 195 of the predicted 225 and 292 amino-acid sequences, respectively. To determine whether this nonsense mutation is genetically associated with the short stature in the family, pedigree analysis was carried out. It was found that all six short individuals (defined as height below 2 standard deviations) showed an aberrant SSCP shift and the cytidine-to-thymidine transition. Neither the father, nor one aunt and maternal grandfather with normal height showed this mutation, indicating that the grandmother has transferred the mutated allele onto two of her daughters and her two grandchildren. Thus, there is concordance between the presence of the mutant allele and the short stature phenotype in this family.

[0091] The identical situation as indicated above was found in another short stature patient of Japanese origin.

Example 8

[0092] The DNA sequences of the present invention are used to characterize the function of the gene or genes. The DNA sequences can be used as search queries for data base searching of nucleic acid or amino acid databases to identify related genes or gene products. The partial amino acid sequence of SHOX93 has been used as a search query of amino acid databases. The search showed very high homology to many known homeobox proteins. The cDNA sequences of the present invention can be used to recombinantly produce the peptide. Various expression systems known to those skilled in the art can be used for recombinant protein production.

[0093] By conventional peptide synthesis (protein synthesis according to the Merrifield method), a peptide having the sequence CSKSFDQKSKDGNGG was synthesized and polyclonal antibodies were derived in both rabbits and chicken according to standard protocols.

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[0094] The following references are herein incorporated by reference.

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[0140] Preferred emobdiments of the invention are especially the following:

E1. An isolated human nucleic acid molecule encoding polypeptides containing a homeobox domain of sixty amino acids having the amino acid sequence of SEQ ID NO: 1 and having regulating activity on human growth.
E2. A nucleic acid molecule according to embodiment E1 which is selected from the following group:

a) an isolated DNA molecule comprising a nucleotide sequence (i) encoding a polypeptide containing a homeobox domain of sixty amino acids having the amino acid sequence of SEQ ID NO: 1 and which has the biological activity to regulate human growth, or (ii) encoding a polypeptide containing a homeobox domain of sixty amino acids having the amino acid sequence of SEQ ID NO: 1 except that one or more amino acid residues have been deleted, added or substituted but which retains the same biological activity of regulating human growth;
b) an isolated DNA molecule comprising the nucleotide sequence of SHOX ET93 [SEQ ID NO: 2] and the nucleotide sequence of SHOX ET45 [SEQ ID NO: 4] or fragments thereof;
c) nucleic acid molecules capable of hybridizing to the DNA molecules of a) or b); and
d) DNA molecules comprising a nucleotide sequence having a homology of seventy percent or higher with the DNA molecules of a) or b).

E3. A DNA molecule according to embodiment E2 which encodes a polypeptide having an N-terminal and/or C-terminal amino acid extension to the homeobox domain of sixty amino acids of SEQ ID NO: 1.
E4. A DNA molecule according to embodiment E3 which encodes a polypeptide having a length of 150 to 350 amino acids.
E5. A DNA molecule according to any of embodiments E2 - E4 further comprising the nucleotide sequence of SHOX G310 [SEQ ID NO: 3].
E6. A DNA molecule according to any of embodiments 2 - 5 further comprising the nucleotide sequence of SHOX G108 [SEQ ID NO: 5].
E7. A DNA molecule according to any of embodiments E2 - E6 further comprising the nucleotide sequence of SHOX Va [SEQ ID NO: 6] or SHOX Vb [SEQ ID NO: 7].
E8. A DNA molecule according to any of embodiments E1 - E4 which encodes a polypeptide which is selected from the following group:

a) transcription factor A having essentially the amino acid sequence of [SEQ ID NO: 11];
b) transcription factor B having essentially the amino acid sequence of [SEQ ID NO: 13]; and
c) transcription factor C having essentially the amino acid sequence of [SEQ ID NO: 16].

E9. DNA sequence comprising the nucleotide sequence of SHOX ET93 [SEQ ID No. 2].
E10. A DNA sequence according to embodiment E9 further comprising the nucleotide sequence of SHOX G310 [SEQ. ID NO. 3].
E11. A DNA sequence according to embodiments E9 or E10 further comprising the nucleotide sequence of SHOX ET45 [SEQ ID NO. 4].
E12. A DNA sequence according to any of embodiments E9 - E12 further comprising the nucleotide sequence of SHOX G108 [SEQ ID 5].
E13. A DNA sequence according to any of embodiments E9 - E12 further comprising either the nucleotide sequence of SHOX Va [SEQ ID 6] or SHOX Vb [SEQ ID 7].
E14. A DNA sequence according to embodiment E9 comprising the nucleotide sequence of SHOX ET93 [SEQ ID

No. 2] and the nucleotide sequence of SHOX ET45 [SEQ. ID. No. 4].

E15. A DNA sequence according to embodiment E9 comprising the nucleotide sequence of SHOX ET93 [SEQ ID NO 2], the nucleotide sequence of SHOX ET45 [SEQ. ID. No. 4] and the nucleotide sequence of SHOX G108 [SEQ ID 5].

E16. A DNA sequence according to any of embodiments E9 - E15 comprising the nucleotide sequences of SHOX G310 [SEQ ID NO. 3], SHOX ET93 [SEQ ID NO 2], SHOX ET45 [SEQ ID No. 4] and SHOX G108[SEQ ID 5].

E17. A DNA sequence according to embodiment 17 further comprising the nucleotide sequence of SHOX Va [SEQ ID No 6].

E18. A DNA sequence according to embodiment E16 further comprising the nucleotide sequence of SHOX Vb [SEQ ID No. 7].

E19. A DNA sequence according to embodiment E9 consisting essentially of the isolated genomic sequence of the PAR1 region identified in [SEQ ID No. 14].

E20. A DNA sequence comprising the nucleotide sequence of SHOX ET92 [SEQ. ID No. 9].

E21. A DNA sequence according to any of embodiments E9 - E20 whereby the DNA is a genomic or isolated DNA responsible for regulating human growth.

E22. A DNA sequence according to any of embodiments E9 - E21 whereby the DNA is a cDNA.

E23. A cDNA according to embodiment E22 consisting essentially of the nucleotide sequence of SHOXa [SEQ ID No. 10] or SHOXb [SEQ ID NO. 12].

E24. A cDNA according to embodiment E22 consisting essentially of the nucleotide sequence of SHOT [SEQ ID No. 14].

E25. A human growth protein (transcription factor SHOXa) having the amino acid sequence given in [SEQ ID No. 11] or a functional fragment thereof.

E26. A human growth protein (transcription factor SHOXb) having the amino acid sequence given in [SEQ ID No. 13] or a functional fragment thereof.

E27. A human growth protein (transcription factor SHOT) having the amino acid sequence given in [SEQ ID NO: 16] or a functional fragment thereof.

E28. A cDNA encoding for a protein according to embodiment E25, E26 or E27.

E29. A pharmaceutical composition comprising a protein according to any of embodiments E25 to E27.

E30. A method for the treatment of short stature comprising administering to a subject in need thereof a therapeutically effictive amount of a protein according to embodiment E25 to E27.

E31. Use of a protein according to embodiment E25 to E27 for the preparation of a pharmaceutical composition for the treatment of short stature.

E32. Use of a DNA sequence according to embodiments E1 - E24 for the preparation of a pharmaceutical composition for the treatment of disorders relating to mutations of the short stature gene.

E33. Use of a DNA sequence according to any of embodiments E1 - E24 for the preparation of a kit for the identification of individuals having a genetic defect responsible for deminished human growth.

E34. Use of a DNA sequence according to embodiment E33 for the identification of a gene responsible for short human stature.

E35. Method for the determination of short stature on the basis of RNA or DNA molecules, wherein the biological sample molecule to be examined is amplified in the presence of two nucleotide probes completely or in part complementary to any of the DNA sequences mentioned in SEQ ID No. 2 to SEQ ID No. 7 and subsequently determined by a suitable detection system.

E36. Use of the method according to embodiment E35 for the identification of persons having a genetic defect responsible for short stature.

E37. Transgenic animal transformed with a gene responsible for short stature containing a DNA sequence according to any one of embodiments E1 - E24.

E38. Cells transformed with a DNA sequence according to any one of embodiments E1 - E24.

E39. Test system for identifying or screening pharmaceutical agents useful for the treatment of human short stature comprising a cell according to embodiment E38.

E40. Method for identifying or screening of candidates for pharmaceutical agents useful for the treatment of disorders relating to mutations in the short stature gene comprising providing a test system according to embodiment E39 and determining variations in the phenotype of said cells or variations in the expression products of said cells after contacting said cells with said candidate pharmaceutical agents.

E41. An expression vector comprising a DNA molecule according to embodiments E1 - E8 which is capable of effecting the expression of the encoded polypeptide.

E42. A method for the *in vivo* treatment of human growth disorders related to at least one mutation in the SHOX or SHOT gene by gene therapy, comprising introducing into human cells an expression plasmid in which a DNA molecule according to any of embodiments E1 - E8 is incorporated downstream from the expression promotor that

effects expression in a human host cell.

E43. A method according to embodiment E42 for the treatment of Turner syndrome or short stature.

E44. Antibodies obtained by immunization of mammals using the transcription factors A, B or C or antigenic fragments thereof and isolating such antibodies from such mammals.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

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(ii) TITLE OF INVENTION: HUMAN GROWTH GENE AND SHORT STATURE GENE REGION

(iii) NUMBER OF SEQUENCES: 16

(iv) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPO)

(vi) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: US 60/027,633
(B) FILING DATE: 01-OCT-1996

(vi) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: EP 97100583.0
(B) FILING DATE: 16-JAN-1997

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

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            20                  25                  30

Glu Leu Ser Gln Arg Leu Gly Leu Ser Glu Ala Arg Val Gln Val Trp
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Phe Gln Asn Arg Arg Ala Lys Cys Arg Lys Gln Glu
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(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
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(v) FRAGMENT TYPE: linear

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(D) TOPOLOGY: linear

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(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

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(A) LENGTH: 89 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "exon IV: G108"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

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(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

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(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:
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(B) TYPE: nucleic acid
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(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
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(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:
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(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
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(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "HOX93"

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1498..1807
(D) OTHER INFORMATION:/function= "part of exon I (G310)"

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(A) NAME/KEY: misc_feature
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(D) OTHER INFORMATION:/function= "part of exon II (ET93)"

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(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 753 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "ET92 gene segment"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

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(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1890 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

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(A) DESCRIPTION:   /desc = "SHOXa"

(ix) FEATURE:
     (A) NAME/KEY: CDS
     (B) LOCATION:91..968

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

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                                 Met Glu Glu Leu Thr Ala Phe Val
                                   1               5

TCC AAG TCT TTT GAC CAG AAA AGC AAG GAC GGT AAC GGC GGA GGC GGA      162
Ser Lys Ser Phe Asp Gln Lys Ser Lys Asp Gly Asn Gly Gly Gly Gly
     10                  15                  20

GGC GGC GGA GGT AAG AAG GAT TCC ATT ACG TAC CGG GAA GTT TTG GAG      210
Gly Gly Gly Gly Lys Lys Asp Ser Ile Thr Tyr Arg Glu Val Leu Glu
 25                  30                  35                  40

AGC GGA CTG GCG CGC TCC CGG GAG CTG GGG ACG TCG GAT TCC AGC CTC      258
Ser Gly Leu Ala Arg Ser Arg Glu Leu Gly Thr Ser Asp Ser Ser Leu
                 45                  50                  55

CAG GAC ATC ACG GAG GGC GGC GGC CAC TGC CCG GTG CAT TTG TTC AAG      306
Gln Asp Ile Thr Glu Gly Gly Gly His Cys Pro Val His Leu Phe Lys
             60                  65                  70

GAC CAC GTA GAC AAT GAC AAG GAG AAA CTG AAA GAA TTC GGC ACC GCG      354
Asp His Val Asp Asn Asp Lys Glu Lys Leu Lys Glu Phe Gly Thr Ala
         75                  80                  85

AGA GTG GCA GAA GGG ATT TAT GAA TGC AAA GAG AAG CGC GAG GAC GTG      402
Arg Val Ala Glu Gly Ile Tyr Glu Cys Lys Glu Lys Arg Glu Asp Val
     90                  95                 100

AAG TCG GAG GAC GAG GAC GGG CAG ACC AAG CTG AAA CAG AGG CGC AGC      450
Lys Ser Glu Asp Glu Asp Gly Gln Thr Lys Leu Lys Gln Arg Arg Ser
105                 110                 115                 120

CGC ACC AAC TTC ACG CTG GAG CAG CTG AAC GAG CTC GAG CGA CTC TTC      498
Arg Thr Asn Phe Thr Leu Glu Gln Leu Asn Glu Leu Glu Arg Leu Phe
                125                 130                 135

GAC GAG ACC CAT TAC CCC GAC GCC TTC ATG CGC GAG GAG CTC AGC CAG      546
Asp Glu Thr His Tyr Pro Asp Ala Phe Met Arg Glu Glu Leu Ser Gln
            140                 145                 150

CGC CTG GGG CTC TCC GAG GCG CGC GTG CAG GTT TGG TTC CAG AAC CGG      594
Arg Leu Gly Leu Ser Glu Ala Arg Val Gln Val Trp Phe Gln Asn Arg
        155                 160                 165

AGA GCC AAG TGC CGC AAA CAA GAG AAT CAG ATG CAT AAA GGC GTC ATC      642
Arg Ala Lys Cys Arg Lys Gln Glu Asn Gln Met His Lys Gly Val Ile
    170                 175                 180

TTG GGC ACA GCC AAC CAC CTA GAC GCC TGC CGA GTG GCA CCC TAC GTC      690
Leu Gly Thr Ala Asn His Leu Asp Ala Cys Arg Val Ala Pro Tyr Val
185                 190                 195                 200

AAC ATG GGA GCC TTA CGG ATG CCT TTC CAA CAG GTC CAG GCT CAG CTG      738
Asn Met Gly Ala Leu Arg Met Pro Phe Gln Gln Val Gln Ala Gln Leu
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                    205                 210                 215

CAG CTG GAA GGC GTG GCC CAC GCG CAC CCG CAC CTG CAC CCG CAC CTG        786
Gln Leu Glu Gly Val Ala His Ala His Pro His Leu His Pro His Leu
                220                 225                 230

GCG GCG CAC GCG CCC TAC CTG ATG TTC CCC CCG CCG CCC TTC GGG CTG        834
Ala Ala His Ala Pro Tyr Leu Met Phe Pro Pro Pro Pro Phe Gly Leu
            235                 240                 245

CCC ATC GCG TCG CTG GCC GAG TCC GCC TCG GCC GCC GCC GTG GTC GCC        882
Pro Ile Ala Ser Leu Ala Glu Ser Ala Ser Ala Ala Ala Val Val Ala
    250                 255                 260

GCC GCC GCC AAA AGC AAC AGC AAG AAT TCC AGC ATC GCC GAC CTG CGG        930
Ala Ala Ala Lys Ser Asn Ser Lys Asn Ser Ser Ile Ala Asp Leu Arg
265                 270                 275                 280

CTC AAG GCG CGG AAG CAC GCG GAG GCC CTG GGG CTC TG ACCCGCCGCG          978
Leu Lys Ala Arg Lys His Ala Glu Ala Leu Gly Leu
                285                 290

CAGCCCCCCG CGCGCCCGGA CTCCCGGGCT CCGCGCACCC CGCCTGCACC GCGCGTCCTG    1038

CACTCAACCC CGCCTGGAGC TCCTTCCGCG GCCACCGTGC TCCGGGCACC CCGGGAGCTC    1098

CTGCAAGAGG CCTGAGGAGG GAGGCTCCCG GGACCGTCCA CGCACGACCC AGCCAGACCC    1158

TCGCGGAGAT GGTGCAGAAG GCGGAGCGGG TGAGCGGCCG TGCGTCCAGC CCGGGCCTCT    1218

CCAAGGCTGC CCGTGCGTCC TGGGACCCTG GAGAAGGGTA AACCCCCGCC TGGCTGCGTC    1278

TTCCTCTGCT ATACCCTATG CATGCGGTTA ACTACACACG TTTGGAAGAT CCTTAGAGTC    1338

TATTGAAACT GCAAAGATCC CGGAGCTGGT CTCCGATGAA AATGCCATTT CTTCGTTGCC    1398

AACGATTTTC TTTACTACCA TGCTCCTTCC TTCATCCCGA GAGGCTGCGG AACGGGTGTG    1458

GATTTGAATG TGGACTTCGG AATCCCAGGA GGCAGGGGCC GGGCTCTCCT CCACCGCTCC    1518

CCCGGAGCCT CCCAGGCAGC AATAAGGAAA TAGTTCTCTG GCTGAGGCTG AGGACGTGAA    1578

CCGCGGGCTT TGGAAAGGGA GGGGAGGGAG ACCCGAACCT CCCACGTTGG GACTCCCACG    1638

TTCCGGGGAC CTGAATGAGG ACCGACTTTA TAACTTTTCC AGTGTTTGAT TCCCAAATTG    1698

GGTCTGGTTT TGTTTTGGAT TGGTATTTTT TTTTTTTTTT TTTTTTGCTG TGTTACAGGA    1758

TTCAGACGCA AAAGACTTGC ATAAGAGACG GACGCGTGGT TGCAAGGTGT CATACTGATA    1818

TGCAGCATTA ACTTTACTGA CATGGAGTGA AGTGCAATAT TATAAATATT ATAGATTAAA    1878

AAAAAAATAG CA                                                         1890
```

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 292 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

```
Met Glu Glu Leu Thr Ala Phe Val Ser Lys Ser Phe Asp Gln Lys Ser
  1               5                  10                  15
```

```
Lys Asp Gly Asn Gly Gly Gly Gly Gly Gly Gly Gly Lys Lys Asp Ser
            20                  25                  30

Ile Thr Tyr Arg Glu Val Leu Glu Ser Gly Leu Ala Arg Ser Arg Glu
        35                  40                  45

Leu Gly Thr Ser Asp Ser Ser Leu Gln Asp Ile Thr Glu Gly Gly Gly
    50                  55                  60

His Cys Pro Val His Leu Phe Lys Asp His Val Asp Asn Asp Lys Glu
65                  70                  75                      80

Lys Leu Lys Glu Phe Gly Thr Ala Arg Val Ala Glu Gly Ile Tyr Glu
                85                  90                  95

Cys Lys Glu Lys Arg Glu Asp Val Lys Ser Glu Asp Glu Asp Gly Gln
            100                 105                 110

Thr Lys Leu Lys Gln Arg Arg Ser Arg Thr Asn Phe Thr Leu Glu Gln
        115                 120                 125

Leu Asn Glu Leu Glu Arg Leu Phe Asp Glu Thr His Tyr Pro Asp Ala
    130                 135                 140

Phe Met Arg Glu Glu Leu Ser Gln Arg Leu Gly Leu Ser Glu Ala Arg
145                 150                 155                     160

Val Gln Val Trp Phe Gln Asn Arg Arg Ala Lys Cys Arg Lys Gln Glu
                165                 170                 175

Asn Gln Met His Lys Gly Val Ile Leu Gly Thr Ala Asn His Leu Asp
            180                 185                 190

Ala Cys Arg Val Ala Pro Tyr Val Asn Met Gly Ala Leu Arg Met Pro
        195                 200                 205

Phe Gln Gln Val Gln Ala Gln Leu Gln Leu Glu Gly Val Ala His Ala
    210                 215                 220

His Pro His Leu His Pro His Leu Ala Ala His Ala Pro Tyr Leu Met
225                 230                 235                     240

Phe Pro Pro Pro Pro Phe Gly Leu Pro Ile Ala Ser Leu Ala Glu Ser
                245                 250                 255

Ala Ser Ala Ala Ala Val Val Ala Ala Ala Ala Lys Ser Asn Ser Lys
            260                 265                 270

Asn Ser Ser Ile Ala Asp Leu Arg Leu Lys Ala Arg Lys His Ala Glu
        275                 280                 285

Ala Leu Gly Leu
    290
```

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 1354 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
- (A) DESCRIPTION: /desc = "SHOXb"

```
(ix) FEATURE:
     (A) NAME/KEY: CDS
     (B) LOCATION:91..768

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

GTGATCCACC CGCCGCACGG GCCGTCCTCT CCGCGCGGGG AGACGCGCGC ATCCACCAGC      60

CCCGGCTGCT CGCCAGCCCC GGCCCCAGCC ATG GAA GAG CTC ACG GCT TTT GTA     114
                                 Met Glu Glu Leu Thr Ala Phe Val
                                             295                 300

TCC AAG TCT TTT GAC CAG AAA AGC AAG GAC GGT AAC GGC GGA GGC GGA     162
Ser Lys Ser Phe Asp Gln Lys Ser Lys Asp Gly Asn Gly Gly Gly Gly
                305                 310                 315

GGC GGC GGA GGT AAG AAG GAT TCC ATT ACG TAC CGG GAA GTT TTG GAG     210
Gly Gly Gly Gly Lys Lys Asp Ser Ile Thr Tyr Arg Glu Val Leu Glu
            320                 325                 330

AGC GGA CTG GCG CGC TCC CGG GAG CTG GGG ACG TCG GAT TCC AGC CTC     258
Ser Gly Leu Ala Arg Ser Arg Glu Leu Gly Thr Ser Asp Ser Ser Leu
        335                 340                 345

CAG GAC ATC ACG GAG GGC GGC GGC CAC TGC CCG GTG CAT TTG TTC AAG     306
Gln Asp Ile Thr Glu Gly Gly Gly His Cys Pro Val His Leu Phe Lys
    350                 355                 360

GAC CAC GTA GAC AAT GAC AAG GAG AAA CTG AAA GAA TTC GGC ACC GCG     354
Asp His Val Asp Asn Asp Lys Glu Lys Leu Lys Glu Phe Gly Thr Ala
365                 370                 375                 380

AGA GTG GCA GAA GGG ATT TAT GAA TGC AAA GAG AAG CGC GAG GAC GTG     402
Arg Val Ala Glu Gly Ile Tyr Glu Cys Lys Glu Lys Arg Glu Asp Val
                385                 390                 395

AAG TCG GAG GAC GAG GAC GGG CAG ACC AAG CTG AAA CAG AGG CGC AGC     450
Lys Ser Glu Asp Glu Asp Gly Gln Thr Lys Leu Lys Gln Arg Arg Ser
            400                 405                 410

CGC ACC AAC TTC ACG CTG GAG CAG CTG AAC GAG CTC GAG CGA CTC TTC     498
Arg Thr Asn Phe Thr Leu Glu Gln Leu Asn Glu Leu Glu Arg Leu Phe
        415                 420                 425

GAC GAG ACC CAT TAC CCC GAC GCC TTC ATG CGC GAG GAG CTC AGC CAG     546
Asp Glu Thr His Tyr Pro Asp Ala Phe Met Arg Glu Glu Leu Ser Gln
    430                 435                 440

CGC CTG GGG CTC TCC GAG GCG CGC GTG CAG GTT TGG TTC CAG AAC CGG     594
Arg Leu Gly Leu Ser Glu Ala Arg Val Gln Val Trp Phe Gln Asn Arg
445                 450                 455                 460

AGA GCC AAG TGC CGC AAA CAA GAG AAT CAG ATG CAT AAA GGC GTC ATC     642
Arg Ala Lys Cys Arg Lys Gln Glu Asn Gln Met His Lys Gly Val Ile
                465                 470                 475

TTG GGC ACA GCC AAC CAC CTA GAC GCC TGC CGA GTG GCA CCC TAC GTC     690
Leu Gly Thr Ala Asn His Leu Asp Ala Cys Arg Val Ala Pro Tyr Val
            480                 485                 490

AAC ATG GGA GCC TTA CGG ATG CCT TTC CAA CAG ATG GAG TTT TGC TCT     738
Asn Met Gly Ala Leu Arg Met Pro Phe Gln Gln Met Glu Phe Cys Ser
        495                 500                 505

TGT CGC CCA GGC TGG AGT ATA ATG GCA TGA TCTCGACTCA CTGCAACCTC      788
Cys Arg Pro Gly Trp Ser Ile Met Ala  *
```

510 515

CGCCTCCCGA GTTCAAGCGA TTCTCCTGCC TCAGCCTCCC GAGTAGCTGG GATTACAGGT 848

GCCCACCACC ATGTCAAGAT AATGTTTGTA TTTTCAGTAG AGATGGGGTT TGACCATGTT 908

GGCCAGGCTG GTCTCGAACT CCTGACCTCA GGTGATCCAC CCGCCTTAGC CTCCCAAAGT 968

GCTGGGATGA CAGGCGTGAG CCCCTGCGCC CGGCCTTTGT AACTTTATTT TTAATTTTTT 1028

TTTTTTTTTA AGAAAGACAG AGTCTTGCTC TGTCACCCAG GCTGGAGCAC ACTGGTGCGA 1088

TCATAGCTCA CTGCAGCCTC AAACTCCTGG GCTCAAGCAA TCCTCCCACC TCAGCCTCCT 1148

GAGTAGCTGG GACTACAGGC ACCCACCACC ACACCCAGCT AATTTTTTTG ATTTTTACTA 1208

GAGACGGGAT CTTGCTTTGC TGCTGAGGCT GGTCTTGAGC TCCTGAGCTC CAAAGATCCT 1268

CTCACCTCCA CCTCCCAAAG TGTTAGAATT ACAAGCATGA ACCACTGCCC GTGGTCTCCA 1328

AAAAAAGGAC TGTTACGTGG AAAAAA 1354

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 226 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

Met Glu Glu Leu Thr Ala Phe Val Ser Lys Ser Phe Asp Gln Lys Ser
1 5 10 15

Lys Asp Gly Asn Gly Gly Gly Gly Gly Gly Gly Gly Lys Lys Asp Ser
20 25 30

Ile Thr Tyr Arg Glu Val Leu Glu Ser Gly Leu Ala Arg Ser Arg Glu
35 40 45

Leu Gly Thr Ser Asp Ser Ser Leu Gln Asp Ile Thr Glu Gly Gly Gly
50 55 60

His Cys Pro Val His Leu Phe Lys Asp His Val Asp Asn Asp Lys Glu
65 70 75 80

Lys Leu Lys Glu Phe Gly Thr Ala Arg Val Ala Glu Gly Ile Tyr Glu
85 90 95

Cys Lys Glu Lys Arg Glu Asp Val Lys Ser Glu Asp Glu Asp Gly Gln
100 105 110

Thr Lys Leu Lys Gln Arg Arg Ser Arg Thr Asn Phe Thr Leu Glu Gln
115 120 125

Leu Asn Glu Leu Glu Arg Leu Phe Asp Glu Thr His Tyr Pro Asp Ala
130 135 140

Phe Met Arg Glu Glu Leu Ser Gln Arg Leu Gly Leu Ser Glu Ala Arg
145 150 155 160

Val Gln Val Trp Phe Gln Asn Arg Arg Ala Lys Cys Arg Lys Gln Glu
165 170 175

Asn Gln Met His Lys Gly Val Ile Leu Gly Thr Ala Asn His Leu Asp

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        180                 185                 190
Ala Cys Arg Val Ala Pro Tyr Val Asn Met Gly Ala Leu Arg Met Pro
        195                 200                 205
Phe Gln Gln Met Glu Phe Cys Ser Cys Arg Pro Gly Trp Ser Ile Met
    210                 215                 220
Ala  *
225
```

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32367 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "COSMID: LLNOYCO3'M'34F5"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

```
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TCTCTCTCTC TCTCCATCTC TCTCTCTCCC TGTCTCTCTC TCTCCATCTC CCCGTCTCTC    120
CGTTTCTCTC TCTGCCTCTC CCTGTCTGTC TCTCTCTTTC TGTGTCTTAC ACACACCCCA    180
ACCCACCGTC ACTCATGTCC CCCCACTGCT GTGCCATCTC ACACAAGTTC ACAGCTCAGC    240
TGTCATCCTG GGTCCCCAGG CCCCGCCGGG GAGGAAGATG CGCCGTGGGG TTACGGGAGG    300
AAGGGGACTC CGGGCCTCCT GGTGCCCCAC TTTATTTGCA GAAGGTCCTT GGCAGGAACC    360
GTGACGCGTT TGGTTTCCAG GACTTGGAAA ACGAATTTCA GGTCGCGATG GCGAGCACCG    420
GCTTCCCCTG AAGCACATTC AATAGCGAGA GGCGGGAGGG AGCGAGCAGG AGCATCCCAC    480
CATGAAAACC AAAAACACAA GTATTTTTTT CACCCGGTAA ATACCCCAGA CGCCAGGGTG    540
ACAGCGCGGC GCTAAGGGAG GAGGCCTCGC GCCGGGGTCC GCCGGGATCT GGCGCGGGCG    600
GAAAGAATAT AGATCTTTAC GAACCGGATC TCCCGGGGAC CTGGGCTTCT TTCTGCGGGC    660
GCTGGAGACC CGGGAGGCGG CCCCGGGGAT CCTCGGCCTC CGCCGCCGCC GCCTCCCAAG    720
CGCCCGCGTC CCGGTTTGGG GACACCCGGC CCCTTCTTCT CACTTTCGGG GATTCTCCAG    780
CCGCGTTCCA TCTCACCAAC TCTCCATCCA AGGGCGCGCC GCCACCAACT TGGAGCTCAT    840
CTTCTCCCAA GATCGTGCGT CCCCGGGGCG CCCGGGTCCC CCCCCTCGCC ATCTCAACCC    900
CGGCGCGACC CGGGCGCTTC CTGGAAAGAT CCAGGCGCCG GGCTCTGCGC TCCTCCCGGG    960
AGCGAGGGCG GCCGGACGAC TGGGACCCTC CTCTCTCCAG CCGTGAACTC CTTGTCTCTC   1020
TGTCTCTCTC TGCAGGAAAA CTGGAGTTTG CTTTTCCTCC GGCCACGGAG AGAACGCGGG   1080
TAACCTGTGT GGGGGGCTCG GGCGCCTGCG CCCCCCTCCT GCGCGCGCGC TCTCCCTTCC   1140
AAAAATGGGA TCTTTCCCCC TTCGCACCAA GGTGTACGGA CGCCAAACAG TGATGAAATG   1200
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AGAAGAAAGC CAATTGCCGG CCTGGGGGGT GGGGGAGACA CAGCGTCTCT GCGTGCGTCC 1260
GCCGCGGAGC CCGGAGACCA GTAATTGCAC CAGACAGGCA GCGCATGGGG GGCTGGGCGA 1320
GGTCGCCGCG TATAAATAGT GAGATTTCCA ATGGAAAGGC GTAAATAACA GCGCTGGTGA 1380
TCCACCCGCG CGCACGGGCC GTCCTCTCCG CGCGGGGAGA CGCGCGCATC CACCAGCCCC 1440
GGCTGCTCGC CAGCCCCGGC CCCAGCCATG GAAGAGCTCA CGGCTTTTGT ATCCAAGTCT 1500
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AAGGACCACG TAGACAATGA CAAGGAGAAA CTGAAAGAAT TCGGCACCGC GAGAGTGGCA 1740
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CGCCACGGAG TCGGCCCCGC GCGCCCCTCG CTGTGCACAT TTGCAGCTCC CGTCTCGCCA 1860
GGGTAAGGCC CGGGCCGTCA GGCTTTGCCT AAGAAAGGAA GGAAGGCAGG AGTGGACCCG 1920
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GGCCGCGCGC GTGGGCACCG ACACGGGAAG GTCCCGGGCT GGGGTGGATC CGGGTGGCTG 2040
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CGGCCTGGGT CCTGACGGCT TAGGATGTGT GTTTCTGTCT CTGCCTGTCT GCCTTGTATT 2460
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GCGGAGGTGG CCGGGATCTG GATGGGGCGC GAGGGGCCCC GGGGAAGCTG GCGGCTTCGC 2760
GGGCGCGTCC TAAGTCAAGG TTGTCAGAGC GCAGCCGGTT GTGCGCGGCC CGGGGGAGCT 2820
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AGTAAGAGGC TCAGAGAGAG GGGCTGGCCC CGGGGATCTC TGTGCACACA CGACAACTGG 2940
GCGGCATACA TCTTAAGAAT AAAATGGGCT GGCTGTGTCG GGGCACAGCT GGAGACGGCT 3000
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ATTCGCAGAG TTGAGGTGCG AGGGTGAATG CCCCAAAGGT AATTCTTCCT AAGACTCTGG 3120
GGCTACCTGC TCTCCGGGGC CCTGCATTTG GGGTGTGGAG TGGCCCCGGG AAATAGCCCT 3180
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CGTGTAATTT AAGAGGGTTC GCAGCGCCCG GCGGCCGCTT CTGTGGGGTT GCTTTTTGGT 3480
TGTCCTTCGC AGACACCGTT TTGCTCCTCT GAACTCTCTC TTCTCCCCCT GGCCGTGGAC 3540
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AAAGACCCAG GGCCACAGGA GAGGAGACAG AGAGTCCCCG TTACATTTTC CCCTTGGCTG 3660
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TCATTAGGGC ATCGCGTGCT TCTCATCTGT GCTCAGCAGG CCCGAGATAG GAACAGAGGG 4320
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GACAGGTCAC CAACTACTGG AGATGAGAAA GTGCCATTTT TGGCACACTC TGGTGGGGTA 4560
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CGACGCCTTC ATGCGCGAGG AGCTCAGCCA GCGCCTGGGG CTCTCCGAGG CGCGCGTGCA 5400
GGTAGGAACC CGGGGGCGGG GGCGGGGGGC CCGGAGCCAT CGCCTGGTCC TCGGGAGCGC 5460
ACAGCACGCG TACAGCCACC TGCGCCCGGG CCGCCGCCGT CCCCTTCCCG GAGCGCGGGG 5520
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GGTTCCCCTG GGATTGGTTA TAGGGGCAAC ACATGCAAAC AAAACTTTCC CTGGATTATA 5820
CTTAGGAGAC GAAGCTACAG ATGCGTTTGA TCCAGAGTGT TTTACAAGAT TTTTCATTTA 5880
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CCTGTCCTCT GCTACAAACC ACCCCCTCCT CCCTCCGGCT GTGGGGAGCG CAGGAGCACG 6120
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GAATTCACGC TGCCCCATGA GACCAGGCAC CGGGGGGCGG AGGGGCCTTG GGTGTCCGCA 6240
GAGGGACGGG CGGGCAGAGC CTTCCTCCGC ATTCTAAACA TTCACTTAAA GGTATGAGTT 6300
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(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 806 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "SHOT"

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION:43..615

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

GTGTCCCCGG AGCTGAAAGA TCGCAAAGAG GATGCGAAAG GGATGGAGGA CGAAGGCCAG 60

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GAGAGGCTTT TTGACGAGAC CCACTATCCC GACGCCTTCA TGCGAGAGGA ACTGAGCCAG 180

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CTGCASNCCC TNDDKANMCG TTRCTYHTCM ATTACACTTT GGGACCYCGG GDBAGVCCTT 720

TTNNAGACTT YVATKGGSCW CSCTGGBCCC TBRKGAVVAC TTGSGHYCGR GAACCGAKHT 780

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(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 190 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

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1               5                   10                  15

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Thr His Tyr Pro Asp Ala Phe Met Arg Glu Glu Leu Ser Gln Arg Leu
        35                  40                  45

Gly Leu Ser Glu Ala Arg Val Gln Val Trp Phe Gln Asn Arg Arg Ala
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Lys Cys Arg Lys Gln Glu Asn Gln Leu His Lys Gly Val Leu Ile Gly
65                  70                  75                  80

Ala Ala Ser Gln Phe Glu Ala Cys Arg Val Ala Pro Tyr Val Asn Val
                85                  90                  95

Gly Ala Leu Arg Met Pro Phe Gln Gln Val Gln Ala Gln Leu Gln Leu
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Asp Ser Ala Val Ala His Ala His His His Leu His Pro His Leu Ala
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Ala His Ala Pro Tyr Met Met Phe Pro Ala Pro Pro Phe Gly Leu Pro
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Leu Ala Thr Leu Ala Ala Asp Ser Ala Ser Ala Ala Ser Val Val Ala
145                 150                 155                 160

Ala Ala Ala Ala Ala Lys Thr Thr Ser Lys Asp Ser Ser Ile Ala Asp
                165                 170                 175

Leu Arg Leu Lys Ala Lys Lys His Ala Ala Ala Leu Gly Leu
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Claims

1. A pharmaceutical composition comprising a protein having regulating activity on human growth, whereby the protein is encoded by a nucleic acid molecule comprising the nucleotide sequence SHOX ET93 [SEQ ID NO: 2] and a nucleotide sequence selected from the group consisting of SHOX G310 [SEQ ID NO: 3], SHOX ET45 [SEQ ID NO: 4], SHOX G108 [SEQ ID NO: 5], SHOX Va [SEQ ID NO: 6] and SHOX Vb [SEQ ID NO: 7] or the nucleotide sequence of SHOT [SEQ ID No.15].

2. A pharmaceutical composition according to claim 1 comprising a protein having the amino acid sequence of SHOXa [SEQ ID NO: 11].

3. A pharmaceutical composition according to claim 1 comprising a protein having the amino acid sequence of SHOXb [SEQ ID NO: 13].

4. A pharmaceutical composition according to claim 1 comprising a protein having the amino acid sequence of SHOT [SEQ ID NO: 16]

5. Use of a protein having regulating activity on human growth, whereby the protein is encoded by a nucleic acid molecule comprising the nucleotide sequence SHOX ET93 [SEQ ID NO: 2] and a nucleotide sequence selected from the group consisting of SHOX G310 [SEQ ID NO: 3], SHOX ET45 [SEQ ID NO: 4], SHOX G108 [SEQ ID NO: 5], SHOX Va [SEQ ID NO: 6] and SHOX Vb [SEQ ID NO: 7], or the nucleotide sequence of SHOT [SEQ ID No. 15] the preparation of a pharmaceutical composition for the treatment of short stature.

6. Use of a protein according to claim 5, the protein having the amino acid sequence of SHOXa [SEQ ID NO: 11].

7. Use of a protein according to claim 5, the protein having the amino acid sequence of SHOXb [SEQ ID NO: 13].

8. Use of a protein according to claim 5, the protein having the amino acid sequence of SHOT [SEQ ID NO: 16].

9. A method for the preparation of a medicament for the *in vivo* treatment of human growth disorders related to a genetic defect in the SHOX or SHOT gene by gene therapy, said SHOX gene having the partial nucleotide sequence as given in [SEQ. ID NO. 8] or having the nucleotide sequence given in [SEQ. ID NO. 14] and said SHOT gene having the nucleotide sequence given in [SEQ. ID NO. 15], the method comprising introducing into an isolated human cell an expression plasmid in which a nucleic acid molecule is incorporated downstream from the expression promotor that effects expression in a human host cell, said nucleic acid molecule comprising the nucleotide sequence SHOX ET93 [SEQ ID NO: 2] and a nucleotide sequence selected from the group consisting of SHOX G310 [SEQ ID NO: 3], SHOX ET45 [SEQ ID NO: 4], SHOX G108 [SEQ ID NO: 5], SHOX Va [SEQ ID NO: 6] and SHOX Vb [SEQ ID NO: 7], or said nucleotide sequence having the seqencence SHOT [SEQ ID NO: 15].

10. A method according to claim 9 whereby the nucleic acid molecule encodes a protein having the amino acid sequence of SHOXa [SEQ ID NO: 11].

11. A method according to claim 9 whereby the nucleic acid molecule encodes a protein having the amino acid sequence of SHOXb [SEQ ID NO: 13].

12. A method according to claim 9 whereby the nucleic acid molecule encodes a protein having the amino acid sequence of SHOT [SEQ ID NO: 16].

13. Use of a human growth protein for the preparation of medicaments for the treatment of patients being suspected of having a genetic defect in the human growth gene SHOX, said SHOX gene having the partial nucleotide sequence as given in [SEQ ID NO: 8].

14. Use of a human growth protein for the preparation of medicaments for the treatment of patients being suspected of having a genetic defect in the human growth gene SHOX, said SHOX gene having the nucleotide sequence as given in [SEQ. ID NO. 14].

15. Use of a human growth protein for the preparation of medicaments for the treatment of patients being suspected of having a genetic defect in the SHOT gene, said SHOT gene having the nucleotide sequence as given in [SEQ.

ID NO. 15].

16. Use of a human growth protein according to claims 13 - 15, said patients being identified of having a genetic defect in the human growth gene SHOX or the SHOT gene using a nucleic acid molecule capable of hybridizing to the SHOX or SHOT gene under the following stringent hybridization conditions: 0.5 M NaPi pH 7.2, 7 % SDS and 1 mM EDTA at 65 °C followed by a wash in 40 mM NaPi and 1 % SDS at 65 °C.

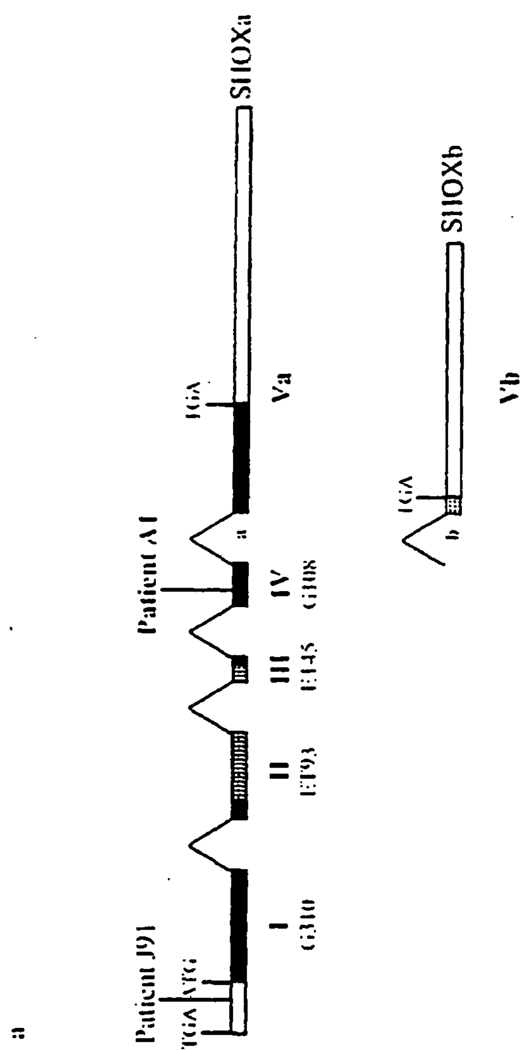
17. Use of a human growth protein for the preparation of medicaments for the treatment of short stature in a human subject having a genetic defect in the SHOX or SHOT gene [SEQ. ID. NO. 15], said SHOX gene having the partial nucleotide sequence as given in [SEQ. ID NO. 8] or having the nucleotide sequence given in [SEQ. ID NO. 14], said human subject being identified by a method comprising determining said genetic defect in a biological sample isolated from said human subject being suspective of having a genetic defect in the SHOX or SHOT gene.

18. Use of a human growth protein according to any of claims 13 - 17 wherein the genetic mutation is caused by a hot spot of mutation in the nucleic acid sequence encoding a protein truncation at amino acid position 195 in the SHOX gene, said SHOX gene having the partial nucleotide sequence as given in [SEQ. ID NO. 8] or having the nucleotide sequence given in [SEQ. ID NO. 14].

19. Use of a human growth protein according to claims 13 - 18 wherein the human growth protein is human growth hormone.

20. Use according to claim 19 with the proviso that the preparation of medicaments for the treatment of patients suffering from Turners Syndrome is excluded.

Fig. 1



SHOXa

Fig. 2

```
1     GTGATCCACCCGCGCGCACGGGCCGTCCTCTCCGCGCGGGGAGACGCGCGCATCCACCAG
61    CCCCGGCTGCTCGCCAGCCCCGGCCCCAGCCATGGAAGAGCTCACGGCTTTTGTATCCAA
1                                        M  E  E  L  T  A  F  V  S  K
121   GTCTTTTGACCAGAAAAGCAAGGACGGTAACGGCGGAGGCGGAGGCGGCGGAGGTAAGAA
11      S  F  D  Q  K  S  K  D  G  N  G  G  G  G  G  G  G  G  K  K
181   GGATTCCATTACGTACCGGGAAGTTTTGGAGAGCGGACTGGCGCGCTCCCGGGAGCTGGG
31      D  S  I  T  Y  R  E  V  L  E  S  G  L  A  R  S  R  E  L  G
241   GACGTCGGATTCCAGCCTCCAGGACATCACGGAGGGCGGCGGCCACTGCCCGGTGCATTT
51      T  S  D  S  S  L  Q  D  I  T  E  G  G  G  H  C  P  V  H  L
301   GTTCAAGGACCACGTAGACAATGACAAGGAGAAACTGAAAGAATTCGGCACCGCGAGAGT
71      F  K  D  H  V  D  N  D  K  E  K  L  K  E  F  G  T  A  R  V
361   GGCAGAAGGGATTTATGAATGCAAAGAGAAGCGCGAGGACGTGAAGTCGGAGGACGAGGA
91      A  E  G  I  Y  E  C  K  E  K  R  E  D  V  K  S  E  D  E  D
421   CGGGCAGACCAAGCTGAAACAGAGGCGCAGCCGCACCAACTTCACGCTGGAGCAGCTGAA
111     G  Q  T  K  L  K  Q  R  R  S  R  T  N  F  T  L  E  Q  L  N
481   CGAGCTCGAGCGACTTTTTGACGAGACCCATTACCCCGACGCCTTCATGCGCGAGGAGCT
131     E  L  E  R  L  F  D  E  T  H  Y  P  D  A  F  M  R  E  E  L
541   CAGCCAGCGCCTGGGGCTTTCCGAGGCGCGCGTGCAGGTTTGGTTCCAGAACCGGAGAGC
151     S  Q  R  L  G  L  S  E  A  R  V  Q  V  W  F  Q  N  R  R  A
601   CAAGTGCCGCAAACAAGAGAATCAGATGCATAAAGGCGTCATCTTGGGCACAGCCAACCA
171     K  C  R  K  Q  E  N  Q  M  H  K  G  V  I  L  G  T  A  N  H
661   CCTAGACGCCTGCCGAGTGGCACCCTACGTCAACATGGGAGCCTTACGGATGCCTTTCCA
191     L  D  A  C  R  V  A  P  Y  V  N  M  G  A  L  R  M  P  F  Q
721   ACAGGTCCAGGCTCAGCTGCAGCTGGAAGGCGTGGCCCACGCGCACCCGCACCTGCACCC
211     Q  V  Q  A  Q  L  Q  L  E  G  V  A  H  A  H  P  H  L  H  P
781   GCACCTGGCGGCGCACGCGCCCTACCTGATGTTCCCCCCGCCGCCCTTCGGGCTGCCCAT
231     H  L  A  A  H  A  P  Y  L  M  F  P  P  P  P  F  G  L  P  I
841   CGCGTCGCTGGCCGAGTCCGCCTCGGCCGCCGCCGTGGTCGCCGCCGCCGCCAAAAGCAA
251     A  L  S  A  E  S  A  S  A  A  A  V  V  A  A  A  A  K  S  N
901   CAGCAAGAATTCCAGCATCGCCGACCTGCGGCTCAAGGCGCGGAAGCACGCGGAGGCCCT
271     S  K  N  S  S  I  A  D  L  R  L  K  A  R  K  H  A  E  A  L
961   GGGGCTCTGACCCGCCGCGCAGCCCCCCGCGCGCCCGGACTCCCGGGCTCCGCGCACCCC
291     G  L  *
1021  GCCTGCACCGCGCGTCCTGCACTCAACCCCGCCTGGAGCTCCTTCCGCGGCCACCGTGCT
1081  CCGGGCACCCCGGGAGCTCCTGCAAGAGGCCTGAGGAGGGAGGCTCCCGGGACCGTCCAC
1141  GCACGACCCAGCCAGACCCTCGCGGAGATGGTGCAGAAGGCGGAGCGGGTGAGCGGCCGT
1201  GCGTCCAGCCCGGGCCTCTCCAAGGCTGCCCGTGCGTCCTGGGACCCTGGAGAAGGGTAA
1261  ACCCCCGCCTGGCTGCGTCTTCCTCTGCTATACCCTATGCATGCGGTTAACTACACACGT
1321  TTGGAAGATCCTTAGAGTCTATTGAAACTGCAAAGATCCCGGAGCTGGTCTCCGATGAAA
1381  ATGCCATTTCTTCGTTGCCAACGATTTTCTTTACTACCATGCTCCTTCCTTCATCCCGAG
1441  AGGCTGCGGAACGGGTGTGGATTTGAATGTGGACTTCGGAATCCCAGGAGGCAGGGGCCG
1501  GGCTCTCCTCCACCGCTCCCCCGGAGCCTCCCAGGCAGCAATAAGGAAATAGTTCTCTGG
1561  CTGAGGCTGAGGACGTGAACCGCGGGCTTTGGAAAGGGAGGGGAGGGAGACCCGAACCTC
1621  CCACGTTGGGACTCCCACGTTCCGGGGACCTGAATGAGGACCGACTTTATAACTTTTCCA
1681  GTGTTTGATTCCCAAATTGGGTCTGGTTTTGTTTTGGATTGGTATTTTTTTTTTTTTTTT
1741  TTTTTGCTGTGTTACAGGATTCAGACGCAAAAGACTTGCATAAGAGACGGACGCGTGGTT
1801  GCAAGGTGTCATACTGATATGCAGCATTAACTTTACTGACATGGAGTGAAGTGCAATATT
1841  ATAAATATTATAGATTAAAAAAAAAAATAGC(A)n
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SHOXb

Fig. 3

```
1     GTGATCCACCCGCGCGCACGGGCCGTCCTCTCCGCGCGGGGAGACGCGCGCATCCACCAG
61    CCCCGGCTGCTCGCCAGCCCCGGCCCCAGCCATGGAAGAGCTCACGGCTTTTGTATCCAA
1                                     M  E  E  L  T  A  F  V  S  K
121   GTCTTTTGACCAGAAAAGCAAGGACGGTAACGGCGGAGGCGGAGGCGGCGGAGGTAAGAA
11     S  F  D  Q  K  S  K  D  G  N  G  G  G  G  G  G  G  G  K  K
181   GGATTCCATTACGTACCGGGAAGTTTTGGAGAGCGGACTGGCGCGCTCCCGGGAGCTGGG
31     D  S  I  T  Y  R  E  V  L  E  S  G  L  A  R  S  R  E  L  G
241   GACGTCGGATTCCAGCCTCCAGGACATCACGGAGGGCGGCGGCCACTGCCCGGTGCATTT
51     T  S  D  S  S  L  Q  D  I  T  E  G  G  G  H  C  P  V  H  L
301   GTTCAAGGACCACGTAGACAATGACAAGGAGAAACTGAAAGAATTCGGCACCGCGAGAGT
71     F  K  D  H  V  D  N  D  K  E  K  L  K  E  F  G  T  A  R  V
361   GGCAGAAGGGATTTATGAATGCAAAGAGAAGCGCGAGGACGTGAAGTCGGAGGACGAGGA
91     A  E  G  I  Y  E  C  K  E  K  R  E  D  V  K  S  E  D  E  D
421   CGGGCAGACCAAGCTGAAACAGAGGCGCAGCCGCACCAACTTCACGCTGGAGCAGCTGAA
111    G  Q  T  K  L  K  Q  R  R  S  R  T  N  F  T  L  E  Q  L  N
481   CGAGCTCGAGCGACTTTTTGACGAGACCCATTACCCCGACGCCTTCATGCGCGAGGAGCT
131    E  L  E  R  L  F  D  E  T  H  Y  P  D  A  F  M  R  E  E  L
541   CAGCCAGCGCCTGGGGCTTTCCGAGGCGCGCGTGCAGGTTTGGTTCCAGAACCGGAGAGC
151    S  Q  R  L  G  L  S  E  A  R  V  Q  V  W  F  Q  N  R  R  A
601   CAAGTGCCGCAAACAAGAGAATCAGATGCATAAAGGCGTCATCTTGGGCACAGCCAACCA
171    K  C  R  K  Q  E  N  Q  M  H  K  G  V  I  L  G  T  A  N  H
661   CCTAGACGCCTGCCGAGTGGCACCCTACGTCAACATGGGAGCCTTACGGATGCCTTTCCA
191    L  D  A  C  R  V  A  P  Y  V  N  M  G  A  L  R  M  P  F  Q
721   ACAGATGGAGTTTTGCTCTTGTCGCCCAGGCTGGAGTATAATGGCATGATCTCGACTCAC
211    Q  M  E  F  C  S  C  R  P  G  W  S  I  M  A  *
781   TGCAACCTCCGCCTCCCGAGTTCAAGCGATTCTCCTGCCTCAGCCTCCCGAGTAGCTGGG
841   ATTACAGGTGCCCACCACCATGTCAAGATAATGTTTGTATTTTCAGTAGAGATGGGGTTT
901   GACCATGTTGGCCAGGCTGGTCTCGAACTCCTGACCTCAGGTGATCCACCCGCCTTAGCC
961   TCCCAAAGTGCTGGATGACAGGCGTGAGCCCCTGCGCCCGGCCTTTGTAACTTTATTTT
1021  TAATTTTTTTTTTTTTTAAGAAAGACAGAGTCTTGCTCTGTCACCCAGGCTGGAGCACA
1081  CTGGTGCGATCATAGCTCACTGCAGCCTCAAACTCCTGGGCTCAAGCAATCCTCCCACCT
1141  CAGCCTCCTGAGTAGCTGGGACTACAGGCACCCACCACCACACCCAGCTAATTTTTTTGA
1201  TTTTTACTAGAGACGGGATCTTGCTTTGCTGCTGAGGCTGGTCTTGAGCTCCTGAGCTCC
1261  AAAGATCCTCTCACCTCCACCTCCCAAAGTGTTAGAATTACAAGCATGAACCACTGCCCG
1321  TGGTCTCCAAAAAAAGGACTGTTACGTGG(A)n
```

Fig. 4

GTGTCCCCGGAGCTGAAAGATCGCAAAGAGGATGCGAAAGGGATGGAGGACGAAGGCCAG
M E D E G Q

ACCAAAATCAAGCAGAGGCGAAGTCGGACCAATTTCACCCTGGAACAACTCAATGAGCTG
T K I K Q R R S R T N F T L E Q L N E L

GAGAGGCTTTTTGACGAGACCCACTATCCCGACGCCTTCATGCGAGAGGAACTGAGCCAG
E R L F D E T H Y P D A F M R E E L S Q

CGACTGGGCCTGTCGGAGGCCCGAGTGCAGGTTTGGTTTCAAAATCGAAGAGCTAAATGT
R L G L S E A R V Q V W F Q N R R A K C

AGAAAACAAGAAAATCAACTCCATAAAGGTGTTCTCATAGGGGCCGCCAGCCAGTTTGAA
R K Q E N Q L H K G V L I G A A S Q F E

GCTTGTAGAGTCGCACCTTATGTCAACGTAGGTGCTTTAAGGATGCCATTTCAGCAGGAT
A C R V A P Y V N V G A L R M P F Q Q D

AGTCATTGCAACGTGACGCCCTTGCCCTTTCAGGTTCAGGCGCAGCTGCAGCTGGACAGC
S H C N V T P L P F Q V Q A Q L Q L D S

GCTGTGGCGCACGCGCACCACCACCTGCATCCGCACCTGGCCGCGCACGCGCCCTACATG
A V A H A H H H L H P H L A A H A P Y M

ATGTTCCCAGCACCGCCCTTCGGACTGCCGCTCGCCACGCTGGCCGCGGATTCGGCTTCC
M F P A P P F G L P L A T L A A D S A S

GCCGCCTCGGTAGTGGCGGCCGCAGCAGCCGCCAAGACCACCAGCAAGGACTCCAGCATC
A A S V V A A A A A A K T T S K D S S I

GCCGATCTCAGACTGAAAGCCAAAAAGCACGCCGCAGCCCTGGGTCTGTGACGCCAACGC
A D L R L K A K K H A A A L G L *

CAGCACCAATGTCGCGCCTGTCCCGCGGCACTCAGCCTGCACGCCCTCCGCGCCCCGCTG
CTTCTCCGTTACCCCTTTGAGACCTCGGGAGCCGGCCCTCTTCCCGCCTCACTGACCATC
CCTCGTCCCCTATCGCATCTTGGACTCGGAAAGCCAGACTCCACGCAGGACCAGGGATCT
CACGAGGCACGCAGGCTCCGTGGCTCCTGCCCGTTTTCCTACTCGAGGGCCTAGAATTGG
GTTTTGTAGGAGCGGGTTTGGGGGAGTCTGGAGAGAGACTGGACAGGGTAGTGCTGGAAC
CGCGGAGTTTGGCTCACCGCAAAGCTACAACGATGGACTCTTGCATAGAAAAAAAAAATC
TTGTTAACAATGAAAAAATGAGCAAACAAAAAAATCGAAAGACAAACGGGAGAGAAAAAG
AGGAAGGCAACTTATTTCTTAACTGCTATTTGGCAGAAGCTGAAATTGGAGAACCAAGGA
GCAAAAACAAATTTTAAAATTAAAGTATTTTATACATTTAAAAATATGGAAAAACAACCC
AGACGATTCTCGAGAGACTGGGGGGAGTTACCAACTTAAATGTGTGTTTTAAAAAATGCG
CTAAGAAGGCAAAGCAGAAAGAAGAGGTATACTTATTTAAAAAACTAAGATGAAAAAAGT
GCGCAGGTGGGAAGTTCACAGGTTTTGAAACTGACCTTTTTCTGCGAAGTTCACGTTAAT
ACGAGAAATTTGATGAGAGAGGCGGGCCTCCTTTTACGTTGAATCAGATGCTTTGAGTTT
AAACCCACCATGTATGGAAGAGCAAGAAAAGAGAAAATATTAAAACGAGGAGAGAGAAAA
ATAATGGCAAAACTGTCTGGACTGCTGACAGTAAATTCCGGTTTGCATGGAAAAAAAAAA
AAAAAAAAAAAAAAAAA

Fig. 5

Exon/Intron Organization of the human SHOX gene

Exon	cDNA-a	cDNA-b	genomic DNA	Exon Size	Intron/Exon	Exon/Intron
I	UTR-368	UTR-368	1-368	368	GTGATCCACC	GTGGCAGAAGgtaagttcct
II	369-577	369-577	3817-4025	209	ccccacgcagGGATTTATGA	GCGCGTGCAGgtaggaaccc
III	578-635	578-635	9851-9908	58	tctccccaagGTTTGGTTCC	ATGCATAAAGgtgggtgtcg
IV	636-724	636-724	10029-10117	89	ttggacacagGCGTCATCTT	TTTCCAACAGgtagctcact
Va	725-1890	----	13364-14529	1166	gctcccgcagGTCCAGGCTC	AAAAAATAGC
Vb	----	725-1349	27154-27778	625	ttttttttagATGGAGTTTT	TGTTACGTGG
polyA	≥ 1891	≥ 1350	----			

Sizes of exons are given in basepairs; exon sequences are shown in capital letters; donor and acceptor splice sites are underlined. Genomic and cDNA sequences are available via GenBank accession no xyz

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

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(12) EUROPEAN PATENT APPLICATION

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05.03.2003 Bulletin 2003/10

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16.01.1997 EP 97100583

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97944906.3 / 0 946 721

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69118 Heidelberg (DE)

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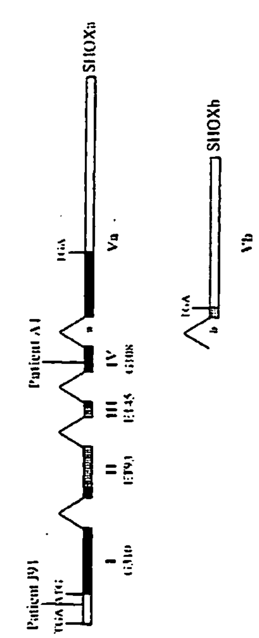
69120 Heidelberg (DE)

(54) **Human growth gene and short stature gene region. Therapeutic uses**

(57) Subject of the present invention is an isolated human nucleic acid molecule encoding polypeptides containing a homeobox domain of sixty amino acids having the amino acid sequence of SEQ ID NO: 1 and having regulating activity on human growth.

Three novel genes residing within the about 500kb short stature critical region on the X and Y chromosome were identified. At least one of these genes is responsible for the short stature phenotype. The cDNA corresponding to this gene may be used in diagnostic tools, and to further characterize the molecular basis for the short stature-phenotype. In addition, the identification of the gene product of the gene provides new means and methods for the development of superior therapies for short stature.

Fig. 1



EP 1 260 228 A3

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PARTIAL EUROPEAN SEARCH REPORT
which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number
EP 02 01 1329

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	THUESTAD INGER JOHANNE ET AL: "Growth hormone treatment in Leri-Weill syndrome." JOURNAL OF PEDIATRIC ENDOCRINOLOGY & METABOLISM, vol. 9, no. 2, March 1996 (1996-03), pages 201-204, XP008011917 * the whole document * ---	13-20	A61K38/18 A61K48/00 A61K38/27
X	DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1988 ROSENFELD R.G. ET AL: "Three-year RESULTS OF A randomized Prospective Trial of Methionyl Human Growth Hormone and oxandrolone in turner syndrome" Database accession no. PREV198886106398 XP002225714 * abstract * & JOURNAL OF PEDIATRICS, ISSN: 0022-3476, vol. 113, no. 2, 1998, pages 393-400, ---	13-19	
	-/--		

TECHNICAL FIELDS SEARCHED (Int.Cl.6)
C07K
C12Q
C12N
A61K

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

Although claims 9-12 (as far as they concern an in vivo method) are directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

Place of search	Date of completion of the search	Examiner
THE HAGUE	20 December 2002	LE CORNEC N.D.R.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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Office

Application Number
EP 02 01 1329

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

☒ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:

☐ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 02 01 1329

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
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			TECHNICAL FIELDS SEARCHED (Int.Cl.6)
A	M. MARRA ET AL: "mj75d03.r1 Soares mouse p3NMF19.5 Mus musculus cDNA clone 481925 5' similar to TR:G1002494 G1002494 ARIX1." EMBL DATABASE ENTRY MMA59929, ACCESSION NUMBER AA059929, 24 September 1996 (1996-09-24), XP002052953 ---		
A	M. MARRA ET AL: "mb68b03.r1 Soares mouse p3NMF19.5 Mus musculus cDNA clone 334541 5'similar to SW: HPR1-chick q05437 homeobox protein PRX-1." EMBL DATABASE ENTRY MM3349, ACCESSION NUMBER W1818334, 4 May 1996 (1996-05-04), XP002052954 ---		
A	L. HILLIER ET AL: "zb81a08.s1 Homo sapiens cDNA clone 309974 3' similar to PIR:S29087 S29087 homeotic protein Otx1-mouse" EMBL DATABASE ENTRY HS100314, ACCESSION NUMBER N99100, 19 April 1996 (1996-04-19), XP002052956 --- -/--		

EPO FORM 1503 03.82 (P04C10)

European Patent Office

LACK OF UNITY OF INVENTION SHEET B

Application Number
EP 02 01 1329

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims: 1-12 totally and 13-18 partially

   Use of SHOXa, SHOXb or SHOT and nucleic acid encoding them in the preparation of pharmaceutical compositions. Gene therapy.

2. Claims: 13-18 partially and 19-20 totally

   Use of a human growth hormone for the preparation of medicaments for the treatment of patients having a genetic defect in the SHOX or SHOT gene.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 02 01 1329

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
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A	DATABASE EMBL [Online] 7 September 1996 (1996-09-07) A.C. ROSCAVELLI ET AL: "Mus musculus OG12b homeodomain protein (OG-12) mRNA, complete cds." retrieved from EBI,HINXTON, UK Database accession no. U67055 XP002215676 * abstract * & A.C. ROSCAVELLI ET AL: "Cloning and characterization of four murine homeobox genes" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA., vol. 93, no. 20, 1 October 1996 (1996-10-01), pages 10691-10696, XP002052968 NATIONAL ACADEMY OF SCIENCE. WASHINGTON., US ISSN: 0027-8424 ---		TECHNICAL FIELDS SEARCHED (Int.Cl.6)
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EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 02 01 1329

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	B.W. SCHÄFER ET AL: "Molecular cloning and characterization of a human PAX-7 cDNA expressed in normal and neoplastic myocytes." NUCLEIC ACIDS RESEARCH., vol. 22, no. 22, 1994, pages 4574-4582, XP002052959 OXFORD GB ---		
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P,A	A.C. ROVESCALLI ET AL: "Cloning and characterization of four murine homeobox genes" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA., vol. 93, 1 October 1996 (1996-10-01), pages 10691-10696, XP002052968 WASHINGTON US * figures 3,4,6 * ---	1-18	

-/--

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PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 02 01 1329

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
T	RAPPOLD G: "SHOX MUTATIONS CAUSE GROWTH FAILURE IN TURNER AND LERI-WEILL SYNDROME" HORMONE RESEARCH, S. KARGER AG, BASEL, CH, vol. 51, no. SUPPL 2, 1999, page 6 XP001002410 ISSN: 0301-0163 ---		
T	VUGUIN P ET AL: "The effect of growth hormone treatment in idiopathic short stature with SHOX mutation" PEDIATRIC RESEARCH, WILLIAMS AND WILKINS, BALTIMORE, MD,, US, vol. 43, no. 4 PART 2, April 1998 (1998-04), page 87A XP002168567 ISSN: 0031-3998 ---		TECHNICAL FIELDS SEARCHED (Int.Cl.6)
T	SCHWARZE C P ET AL: "SHOX GENE MUTATIONS IN CHILDREN WITH IDIOPATHIC SHORT STATURE - SCREENING AND THERAPY WITH RHGH" HORMONE RESEARCH, S. KARGER AG, BASEL, CH, vol. 51, no. SUPPL 2, 1999, page 34 XP001002411 ISSN: 0301-0163 -----		

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